DISSERTATION ON

A STUDY OF CLINICAL PROFILE AND SERUM HOMOCYSTEINE LEVEL IN YOUNG STROKE - EXCLUDING RISK FACTORS SMOKING, ALCOHOL,HYPERCHOLESTEROLEMIA,HYPERTENSION AND DIABETES MELLITUS.

Dissertation submitted to

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In partial fulfillment of the regulations
for the award of the degree of

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(BRANCH – I)

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THANJAVUR - 613 004

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032

APRIL -2015

CERTIFICATE

This is to certify that this dissertation entitled **"A study of clinical profile and serum homocysteine level in young stroke-excluding risk factors smoking, alcohol, hypercholesterolemia, hypertension and diabetes mellitus''** is the bonafide original work of Dr.SATHYASAGAR K in partial fulfilment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu Dr.M.G.R. Medical University to be held in APRIL - 2015. The period of the study was from DECEMBER – 2013 to JUNE -2014.

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DECLARATION

I, **Dr.SATHYASAGAR K**, solemnly declare that dissertation titled **"A Study Of Clinical Profile And Serum Homocysteine Level In Young Stroke-Excluding Risk Factors Smoking, Alcohol, Hypercholesterolemia, Hypertension And Diabetes Mellitus"** is a bonafide work done by me at Thanjavur Medical College, Thanjavur, during DECEMBER - 2013 to JUNE-2014 under the guidance and supervision of **Prof.Dr.S.MANOHARAN, M.D.,** Unit Chief M-3, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.D. Degree (Branch - I) in General Medicine**.

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submitted by Dr. K. SATHYASAGAR **of**

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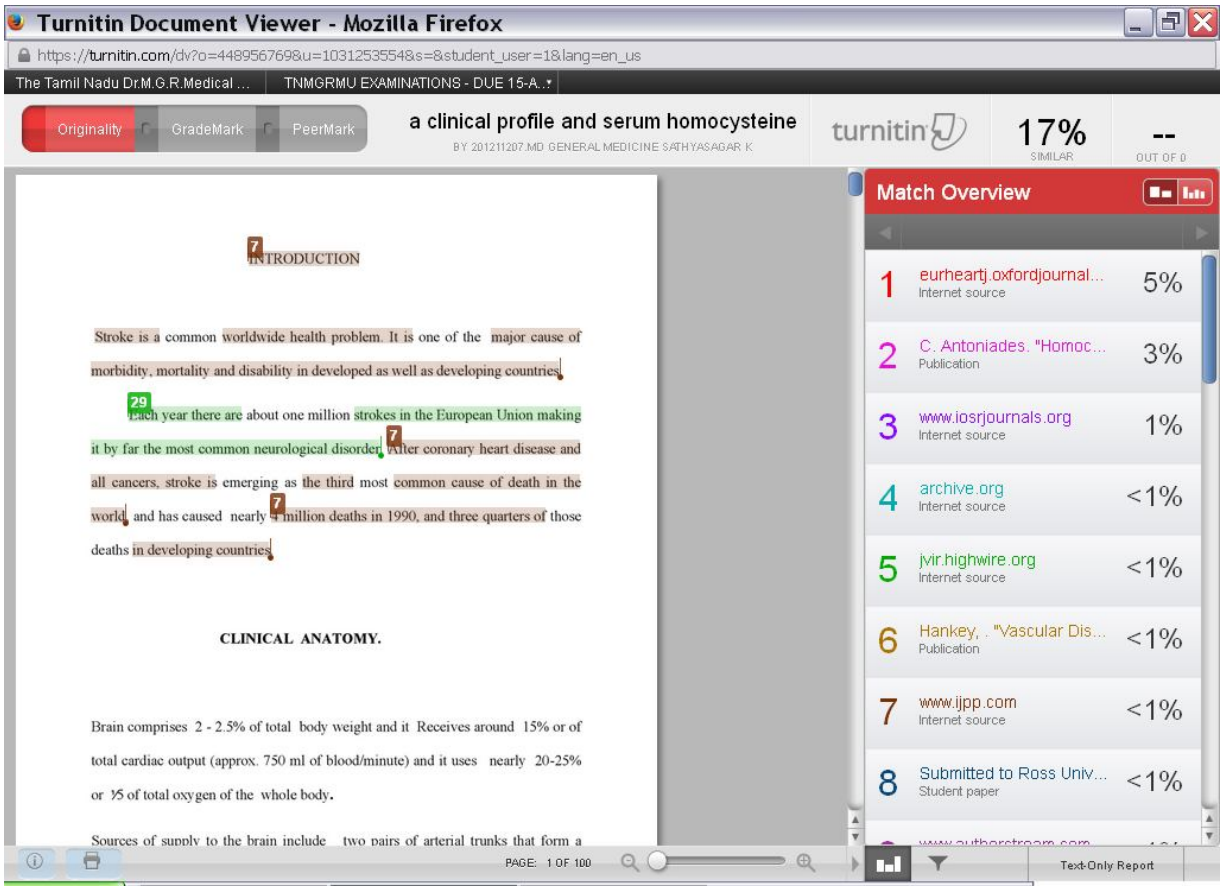
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INTRODUCTION
Stroke is a common worldwide health problem. It is one of the major cause of morbidity, mortality and disability in developed as well as developing countries.
Each year there are about one million strokes in the European Union making it by far the most common neurological disorder. After coronary heart disease and all cancers, stroke is emerging as the third most common cause of death in the world, and has caused nearly 4 million deaths in 1990, and three quarters of those deaths in developing countries.
CLINICAL ANATOMY.
Brain comprises 2 - 2.5% of total body weight and it Receives around 15% or of total cardiac output (approx. 750 ml of blood/minute) and it uses nearly 20-25% or 1/5 of total oxygen of the whole body.
Sources of supply to the brain include two pairs of arterial trunks that form a
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CLINICAL ANATOMY.

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Sources of supply to the brain include two pairs of arterial trunks that form a complex anastomosis (circle of Willis), the Internal carotid artery that applies

ABBREVIATIONS

Cva- Cerebro Vascular Accident

ICH-Intra Cranial Hemorhage

CAD-Coronary Arter Disease

CT-Clotting Time

MRI- Magnetic Resonance Imaging

Hcy- Homocysteine

BT-Bleeding Time

MTHF-Methylene Tetra Hydro Folate

FA- Folic Acid

PCA-Posterior Cerebral Artery

ACA- Anterior Cerebral Artery

ICA- Internal Carotid Artery

NO –Nitrous Oxide

ECM –Extra Cellular Matrix

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A STUDY OF CLINICAL PROFILE AND SERUM HOMOCYSTEINE LEVEL YOUNG STROKE- EXCLUDING RISK FACTORS SMOKING, ALCOHOL,HYPERCHOLESTEROLEMIA,HYPERTENSION, DIABETES MELLITUS

ABSTRACT:

BACKGROUND:

Stroke is a common worldwide health problem. It is one of the major cause of morbidity, mortality and disability in developed as well as developing countries. Each year there are about one million strokes , making it by far the most common neurological disorder. Hyperhomocysteinemia is one of the newly recognized factor that increases the risk of vascular disease. In this study we evaluated the role of serum homocysteine as individual risk factor for young stroke in the absence of smoking, diabetes mellitus, hypercholesterolemia,alcoholism .

Methodology:

50 patients with young stroke were selected for the study. Patients having Conventional risk factor like hypertension ,diabetes mellitus, smoking, hyperlipedemia, alcoholism were excluded from the study. Serum homocysteine was assayed using fluorescence polarization immunoassay.

Results: Of the 50 patients included in the study 32 patients had elevated homocysteine and 18 patients homocysteine were within normal limit. Hence the study shows an increased incidence of stoke in patients with elevated

homocysteine and it was statistically significant. Average serum homocysteine level in patients of young stroke with elevated homocysteine is 34.58 .the average homocysteine level in young stroke patients with normal range homocysteine is 11.8. In our study out of 32 patients with elevated serum homocysteine there was 3% hemorrhagic stroke 13% CVT, and the remaining 84% patients had ischaemic stroke.

Conclusion:

Our study shows hyperhomocystenemia in majority of young stroke patients around 64% who did not have the conventional risk factors . Also patients with hyperhomocysteinemia were more commonly found in the age group of 30-35years and hyperhomocysteinemia as a cause of young stroke was more common among males compared to females. since hyperhomocysteinemia is associated with increased incidence of young stroke and recurrent stroke large group of well organized study studies has to be conducted to find out whether homocysteine lowering therapy with high dose folic acid, pyridoxine and vitamin B12 reduces the incidence of young stroke and recurrent stroke .

Key Words: young stroke, hyperhomocysteinemia, individual risk factor.

INTRODUCTION

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Each year there are about one million strokes in the European Union making it by far the most common neurological disorder. After coronary heart disease and all cancers, stroke is emerging as the third most common cause of death in the world, and has caused nearly 4 million deaths in 1990, and three quarters of those deaths in developing countries.

AIMS AND OBJECTIVES

To assess serum homocysteine level as an individual risk factor for young stroke.

CLINICAL ANATOMY.

Brain comprises 2 - 2.5% of total body weight and it Receives around 15% or of total cardiac output (approx. 750 ml of blood/minute) and it uses nearly 20-25% or ⅕ of total oxygen of the whole body.[1]

Sources of supply to the brain include two pairs of arterial trunks that form a complex anastomosis (circle of Willis), the Internal carotid artery that spplies Forebrain & occipital lobe of cerebrum and the Vertebral artery supplies the Occipital lobe, brainstem & cerebellum, upper spinal cord.

Internal Carotid Artery: figure

It arises from the Bifurcation of common carotid artery Course includes an Extracranial part that enters cranial cavity via carotid canal and an Intracranial S-shape curve called carotid siphon

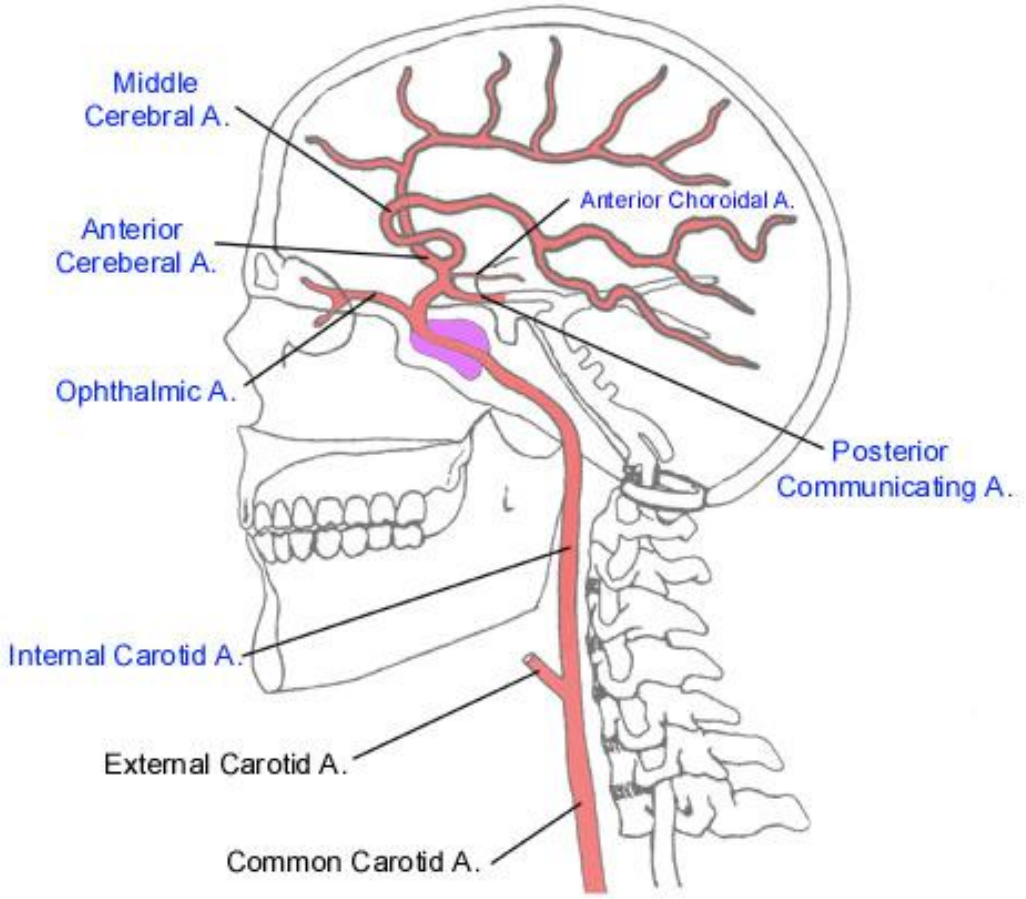


Figure 1

Petrous part of temporal bone , Side of sphenoid & within cavernous sinus in close relation with CN III, IV, V & VI, reaches base of brain lateral to optic chiasm.the cerebral course pierces dura mater to reach anterior perforated space.

The Extracerebral Branches of Internal Carotid Artery are the Petrous part,Caroticotympanic to tympanic cavity ,Pterygoid artery to pterygoid

Canal, Cavernous part Meningeal , Hypophysial . After cavernous course Ophthalmic branch to contents of orbital cavity and 6 Cerebral branches Choroidal ,Anterior cerebral, Middle cerebral artery.

Anterior cerebral artery :

It is a Smaller terminal branch of ICA and it has Cortical branches supplying medial surface and marginal area of superolateral surfaces of cerebrum and the Central branches which supply rostrum of corpus callosum, septum pellucidum, putamen, head of nucleus.

Middle cerebral artery:

It is one of the Larger terminal branch of ICA it has Cortical branches which supply superolateral surface & temporal pole and the Central branches Medial striate which supply caudate nucleus, internal capsule, lentiform nucleus,the Lateral striate branch which supply the caudate nucleus.the Charcot's artery of cerebral haemorrhage – largest & most frequently ruptured in apoplexy.

The vertebral artery :

Its branches include Posterior spinal artery which supply the Dorsal 1/3rd spinal cord .the Anterior spinal which supply the Ventral 2/3rd spinal cord, the Posterior inferior cerebellar Largest branch & supplies cerebellum, the Medullary branches which supply the Medulla oblongata. The Basilar artery: Formed by union of vertebral arteries .Branches of basilar artery include Anterior inferior cerebellar (AICA) which supply the Inferior surface of cerebellum,the Labyrinthine (internal auditory) and

Internal ear,the Pontine branch which supply the pons the Superior cerebellar (SC) artery which spply Superior surface of cerebellum and anastomose with AICA and finally the Posterior cerebral (PC) artey.

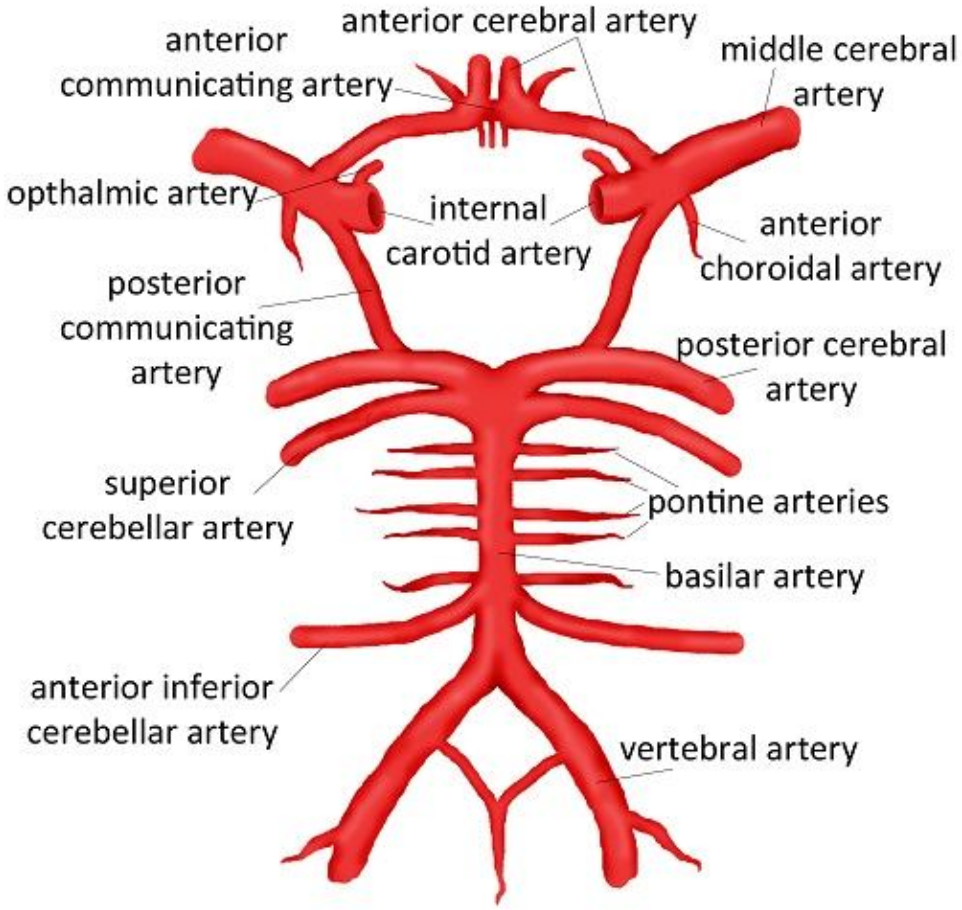
Posterior cerebral artery:

Posterior cerebral is the Terminal branch of basilar artery and its branches includes the Cortical which supplies the inferior surface of cerebrum, occipital pole (visual cortex) the Central branches which supply the thalamus, 3rd ventricle, globus pallidus and the Posterior choriodal arter which supply the choroid plexus of lateral ventricle, thalamus, fornix & tectum of midbrain.

Circle of willis:

Circle of Willis is an Arterial anastomosis connecting vertebrobasilar & internal carotid systems Located at the base of interpeduncular fossa Branches Involved are

Figure 2



1) Anterior communicating artery

2)Anterior cerebral artery

3)Internal carotid artery

4)Posterior communicating artery

5) Posterior cerebral artery.

Importance of circle of Willis: It serves to equalise blood flow to various parts of brain and in maintaining a constant supply of oxygen & glucose even when a contributing artery is narrowed or in head movements .

Furnishes collateral circulation in cases of occlusion of one or more of arteries contributing to circle.

Venous drainage of the brain:

Characteristic Features

1) No valves

2) Extremely thin walls

3) Lack muscular tissue in tunica media

4)Pierce arachnoid mater & inner layer of dura mater

5)End in dural venous sinuses.

HISTORICAL ASPECTS

Hippocrates, called stroke as apoplexy. Because of the fact patients dvelopd sudden inability to use the limbs.

Jaecob vefer discovered that patients with sudden loss of consciousness died of internal hemorhage.later it was found out stroke was very similar to heart attack and was called brain attack .

Today there is enough information about stroke to public which has ultimatel increased awareness of timely recognition immediate medical attention.

HOMOCYSTEINE :

Homocysteine was first discovered in 1932 by Butz and du Vigneaud. As part of their studies into insulin, they heated an amino acid called "methionine" in sulfuric acid. They discovered that doing so changed methionine into a new amino acid which had similar chemical properties to cysteine. They suggested that it should be called homocysteine. Later, du Vigneaud won the 1955 Nobel Prize in Chemistry, partly for his work on this [2]

Inborn Errors of Homocysteine Metabolism

Later Over the next few decades a more clearer picture began to emerge of how the body breaks down or "metabolises" methionine. Homocysteine was identified as an one of the important intermediate. The discovery of patients with inherited or "inborn" errors of homocysteine metabolism gave a valuable insight into the roles of enzymes in this process. It was found that many of these enzymes needed B vitamins, including vitamins $B_{12,}$ B6 and folate, to act as "cofactors" to help them work properly.

STROKE

A stroke, defined as cerebrovascular accident (CVA), cerebrovascular insult (CVI), or colloquially brain attack and it is the loss of brain functions due to a disturbance in the vascular supply to the brain . This may be either due to lack of blood flow or hemorrhage.

Epidemiology:

Prevalence

- One in every ten deaths is due to stroke and is surpassed only by CAD and malignancy.

Stroke in india :

India is facing an increase in stroke burden due to increased in mortality and morbidity due to stroke. Maximum case fatality was fond to be in Kolkata .

Stroke rehabilitation is very poor in india. Rehabilitation centres are in private hospitals and in cities wher the bulk of the poor people cannot afford

Government is organizing various programmes for non ommunicable diseases.

Incidence

- Within 5 years of a stroke, over half of patients aged above 45 years will die: 52% of men and 56% of women.

BURDEN OF STROKE IN INDIA:

The mortality due to stroke is decreasing in india but .As life expectancy is projected to increase in india but the epidemic of stroke is on the rise, India will face economic burden from this rising number of stroke patients. The economc burden of stroke in india has not been exactly accessed but it is estimated that india might have lost billions of rupees due to stroke and more importantl indias GDP is estimated to fall owing to the burden of stroke,coronar diseases.[3]

Some studies in the recent past ndicated the national percapita was a strong indicator of stroke outcome.

PATHOPHYSIOLOGY OF STROKE:

The etiology of stroke involves two major mechanisms ischaemia and hemorhage. In ischemic stroke,which is a major contribtion in stroke etiology ther is decreaed blood and nutrient supply to the brain .brain suffers rapid damage because brain has got no glucose store and hence damge occurs very rapid .another small but next major contribtion of stroke is hemorrhage [4] . Intracerebral hemorrhage arising from deep penetrating vessels causes focal damge and mass effect of the surrounding tissues .

Focal Ischaemic Injury:

A thrombus or even an emboli can obstruct flow in particular vessel causes ischemia. But it is difficult to distinguish between the two causes.

At tissue level stroke is a dynamic process and it evolves into stages .how the stroke progresses and how much amount of damage it has caused depends on its rate of progression .

Collateral circulation:

The presence of collateral circulation influences the outcome of stroke since abundant collaterals minimizes the adverse outcome of stroke.

The Health of systemic circulation:

Cerebral perfusion is autoregulated within a narrow range hence hypotension can compromise cerebral blood flow if it is very severe .

Hematological factors:

Presence of any hypercoagulable state influences the outcome of stroke in an adverse manner

Temperature: increased bod temperatre has poor outcome

Glucose metabolism: hyper- hypoglycemia can have an adverse outcome on the size of infarct and recovery

RISK FACTORS FOR STROKE:

MODIFIABLE RISK FACTORS :

Several very prevalent conditions potentiate the development of atherosclerosis. These conditions can affect almost all persons. The risk of stroke can be reduced if these factors are identified and controlled. Because these conditions are found in all segments of society, their treatment is crucial for an overall reduction in the incidence in stroke. Public health measures to screen and treat these risk factors can be applied to large segments of the general population. Because it is possible to detect some risk factors years before the development of symptomatic atherosclerosis, the effects of education to control risk factors will be greatest when applied to younger asymptomatic persons. Aggressive measures to control the risk factors do have an impact for example, some of the decline in stroke in Canada and United States is attributed to improved treatment of arterial hypertension. The presence of multiple risk factors greatly increases the likelihood of stroke or generalized atherosclerosis. Thus, all common risk factors should be sought and addressed. Control of risk factors is as important for asymptomatic patients in the general population as it is for persons with overt vascular disease. Although management after the

development of ischaemic symptoms focuses on medical or surgical measures to more directly prevent or treat the stroke, control of these risk factors to forestall the evolution of atherosclerosis remains a fundamental component of the overall care of these high-risk patients.[5]

Arterial hypertension :

Arterial hypertension is the leading underlying, potentially treatable condition that promotes stroke.The prevalence of hypertension has not declined since the 1970s. Hypertension is calculated to be a factor in 70% of strokes and among survivors, it identifies a patient as having an increased risk of a second event. The risk of stroke increases 10-12 times if diastolic blood pressure is 105 mmHg in comparison to a normal diastolic blood pressure of approximately 76 mmHg.Overall, arterial hypertension increases the likelihood of stroke. The risk rises rapidly with higher levels of blood pressure. The impact of an increase in diastolic blood pressure is much greater in young adults than in the elderly. Although elevated diastolic blood pressure is a usual marker for hypertension, isolated systolic hypertension also predicts stroke in elderly persons. Isolated systolic hypertension also is correlated with increased thickness and plaque formation of the internal carotid artery. Both elevated diastolic and systolic blood pressures are associated with increased concentrations of hemoglobin,

Chronic hypertension promotes the development of both large-and medium caliber artery atherosclerosis and the lipohyalinosis of small penetrating arteries of the brain. The vascular endothelium is the central focus of the effects of hypertension that promotes turbulence at the site of an atherosclerotic plaque. Thus, hypertension can promote either major arterial occlusion and multilobar infarctions, or small artery occlusions that cause subcortical, lacunar infarctions. The relationship between arterial hypertension and small vessel occlusive disease is so strong that the diagnosis of a lacunar infarction is questioned if the patient does not have a history of hypertension. Because hypertension leads to coronary artery disease, cardiomyopathy, and atrial fibrillation, it is an indirect risk factor for stroke secondary to cardioembolism.

Because hypertension is asymptomatic, it is unrecognized in a sizeable proportion of persons. In addition, many patients with arterial hypertension are not treated adequately.Reducing diastolic blood pressure by approximately 5 mmHg can reduce the incidence of and mortality from stroke by 42% and 30% respectively. In elderly patients, a drop of systolic blood pressure by approximately 11 mmHg can lead to a 30% decline in the frequency of stroke. A report from Asia concluded that a population-wide reduction of 3 mmHg in diastolic blood pressure could reduce the number of strokes by one-third. The optimal levels for blood pressure are 80-85

mmHg diastolic and 130-140 mmHg systolic. Options of treatments include changes in behavior, weight control, increased exercise, dietary modifications, and medications.:

Diabetes mellitus :

Persons with either type I or type II diabetes mellitus have an increased susceptibility for large artery atherosclerosis and small artery occlusive disease.

Diabetes mellitus also leads to renal or cardiac disease, which indirectly promote arterial hypertension and stroke. Diabetes also increase levels of fibrinogen and clotting factors, increase platelet aggregation, which in turn promotes arterial thrombosis. When compared to non-diabetic persons, the risk of stroke increases in proportion to increases in levels of blood glucose especially in young adults. Diabetic patients with stroke are typically younger than patients with stroke who do not have diabetes mellitus. The severity of and mortality after stroke also are higher among patients with diabetes. A markedly elevated level of blood glucose can cause neurological deficits associated with alternations in consciousness. Usually focal signs are not prominent among patients with hyperglycemia. Conversely, hypoglycemia is more common than hyperglycemia in mimicking the symptoms and signs of acute ischaemic stroke.

Prolonged periods of hypoglycemia can lead to neurological sequelae, including cognitive impairments. Thus, prompt treatment of a low serum glucose level is a critical component of urgent care in cases of suspected stroke.

Elevated blood lipids

In the past, the role of elevated blood lipids in the development of ischaemic cerebrovascular disease was unclear largely because advancing age lessened the impact of the condition as a predisposing factor for stroke. In addition, sizeable proportions of strokes that are hemorrhagic or that are not secondary to atherosclerosis were included in the analyses. In fact, the proper analysis is to study the relationship of hyperlipidemia to stroke secondary to atherosclerosis. This analysis could include or exclude cardioembolic strokes secondary to myocardial infarction or ischaemic heart disease.The incidence of coronary artery disease and atherosclerosis of major intracranial or extracranial arteries increases with rising levels of serum cholesterol [6.] Recent data show that hypercholesterolemia is a key risk factor for ischaemic stroke, especially in men under the age of 60. Hyperlipidemia causes a modest increase in risk of stroke in persons older than 62. Some of the risk may be indirect, due to the potent effects of hyperlipidemia on coronary artery disease, leading to myocardial infarction and cardioembolism. The desired levels of total cholesterol, LDL

cholesterol, and HDL cholesterol are <200 mg/dL (5.20 mmol/L), <130 mg/dL (3.36 mmol/L), and >35 mg/dL (0.9 mmol/L), respectively. The risk of stroke is lowest among men with the highest HDL cholesterol levels. Elevated serum apolipoprotein A1 and B concentrations are found in young adults with stroke. The significance of elevated apolipoproteins and stroke is uncertain. The influence of hypertriglyceridemia has not been determined on the course of atherosclerosis.

Obesity :

Overweight men have approximately twice the risk of stroke than thin men.However, obesity is not identified as a primary risk factor for stroke, though an elevated body weight predisposes to vascular disease via its aggravation of arterial hypertension, diabetes mellitus, and heart disease. The risk from obesity appears to be separate from the risk associated with elevated serum cholesterol levels. Thus, obesity should be considered as a contributing factor for stroke. Weight reduction remains a component of general public health activities to lessen the likelihood of ischaemic stroke.

Physical Inactivity

Although physical inactivity is a well known risk factor for coronary artery disease, its relationship to ischaemic stroke is not as apparent.Gillum et al found the strongest relationship between a high risk of stroke and a low level of exercise among younger persons. In addition, exercise decreases the

risk of ischaemic stroke by reducing platelet aggregation and increasing insulin utilization.

Hyperhomocystinemia

Homocysteine has been found to be a potential many vascular catastrophy.it is found in ; folate, pyridoxine, and vitamin B12.increased homocysteine level has been found to be a risk factor for stroke , aortic disease, ischaemic heart disease. It may cause endothelial damage , smooth muscle proliferation, ECM changes , and lipoprotein oxidation in the arterial wall. Homocysteine increases the rate of atherosclerosis and may potentiate the other risk factors like smoking and alcohol in causing vascular damage [7 8 9]

Smoking damages the endothelium, accelerates atherosclerosis, and increases the immune response and cholesterol concentration in arterial walls and decreases endothelial function. It also increases hemoglobin, serum fibrinogen, platelet aggregation, LDL cholesterol, and the hematocrit as it decreases HDL cholesterol levels. Smoking promotes the progression of atherosclerotic plaques of the carotid artery. Similar findings are noted in studying the coronary arteries and the thoracic aorta. Smoking can lead to stroke by aggravating coronary artery disease. Advanced intracranial occlusive disease, causing moyamoya syndrome, also has been associated with smoking, particularly in young women using oral contraceptives.

Although cigarette smoking is most commonly implicated, the use of cigars, pipes, or chewing tobacco also probably increases the risk of atherosclerosis. Chewing tobacco also can be a risk factor for stroke.

Alcohol Use :

Minimal alcohol drinking lessens the risk of vascular events , possibly by increasing the concentration of HDL cholesterol. The definition of mild-to-moderate consumption of alcohol is amorphous but probably is less than 100 gm/week.

Drinking a glass of wine is not an antidote to other dietary indiscretions. Alcohol abuse and acute alcohol intoxication can lead to ischaemic stroke due to alcohol induced cardiomyopathy, changes in viscosity, and disturbances in coagulation and fibrinolytic factors. heavy alcohol drinking on weekends and holidays are related to high risk of vascular events in young persons. Young adults and adolescents should be warned about the increased likelihood of stroke that can occur with heavy alcohol consumption.

Drug Abuse :

The role of drug abuse in the etiology of stroke needs additional definition. Some of the perceived or real increase of stroke in young adults might be

secondary to drug abuse. Abuse of drugs, in particular cocaine and stimulants, can cause stroke.

Persons abusing parenterally administered drugs also have a risk for infective endocarditis that leads to embolism to the brain.

Post-menopausal use of estrogens

Information is limited about the influence of the use of estrogens or estrogen / progesterone medications on the rate of ischaemic stroke in post-menopausal women. At present, the evidence suggests that post-menopausal estrogen supplementation may be helpful. Conversely, there is no evidence that post-menopausal use of estrogens increases the likelihood of ischaemic stroke.

Oral contraceptives

Shortly after the introduction of oral contraceptives, epidemiological studies noted that these medications increased the risk of stroke in young women. Some young women using oral contraceptives may have an increased risk for stroke. The risks seem to be lower in younger women (under age 35) and in those who do not smoke or have hypertension. Use of oral contraceptives has been associated with advanced intracranial occlusive disease (moyamoya syndrome). Recent studies have suggested that oral contraceptives may be a contributing factor for stroke but that their impact

may be marginal. At present, there is no evidence that oral contraceptive use is a major risk factor for stroke in young women.

Migraine:

Various studies been done between migraine and ischaemic stroke and it was found that migrane increased stroke incidenceespeciall in OCP users.

NON MODIFIABLE RISK FACTORS:

Age

Stroke can affect a person at any age. Still, advancing age is the single most important factor that predicts an increased likelihood of ischaemic stroke. Risks increase rapidly after the age of 55 in both men and women of all ethnic groups. The risks of stroke approximately double with every 10-year increase in age.A person's age also influences prognosis. Elderly patients die more often and recover less from stroke than do persons under the age of 65.

Sex

Stroke is an important cause of death and disability in men and women of all age and ethnic groups. In almost all age groups, ischaemic stroke is more common in men than in women except for a slightly higher risk of stroke among women ages 15-30 because cerebrovascular events occur as a complication of pregnancy and the puerperium.

Ethnicity and Geography

Stroke affects all ethnic groups and races in the world. No geographic region of the world is protected from ischaemic stroke.

Epidemiological data are sketchy for estimating accurate rates in most of the Middle East, Africa, South Asia, or Latin America. The types of stroke also vary among ethnic groups; for example, lacunar infarctions are more common in Chinese than other populations. An association of arterial hypertension and ischaemic stroke is stronger in eastern Asian populations, where cholesterol concentrations are very low. Rate are higher in Hispanic Americans than in non-Hispanic white Americans younger than 65, the incidence of stroke is similar in the two groups in older persons. Stroke recurrences are more frequent in African American and Hispanic Americans than among whites. Further research is needed to understand the differences in the rates of stroke, mortality, and risk of recurrences in Americans of different ethnic groups. Some of the differences may be secondary to differences in the prevalence of important risk factors.

The ethnicity of a patient remains important in the evaluation of the risk for stroke. It also is consequential in the determination of the cause of ischaemic stroke and for treatment plans.. A person's marital status is important and regardless of age, married persons have a lower risk of stroke than do single people.

Living alone also affects an individual's likelihood of reaching medical attention quickly after stroke and his or her outcomes after rehabilitation. Family history of vascular disease Ischaemic stroke results from a number of inherited disorders of coagulation or of genetic disorders that predispose to arterial disease. In addition, hereditary disorders, such as diseases of lipid metabolism, can promote premature development of atherosclerosis. Familial predisposition to diabetes mellitus or migraine also may play a role in the development of stroke. A family history of deep vein thrombosis, pulmonary embolism, or spontaneous abortions points to the possibility of a hereditary prothrombotic state.

Ischaemic stroke also appears to peak in the first hours after awakening in the morning. This rise may be secondary to changes in blood pressure or coagulation. These associations and potential responses require further clarification.

NOVEL RISK FACTORS:

1.Excess homocysteine in blood High levels may be associated with an increase in cardiovascular risk.

2.Inflammation :Several inflammatory markers are associated with increased cardiovascular risk, e.g. elevated C-reactive protein (CRP).

3.Abnormal blood coagulation Elevated blood levels of fibrinogen and other markers of blood clotting increase the risk of cardiovascular complications.

TYPES OF STROKE:

ISCHAEMIC STROKE :

Acute ischaemic stroke involves a rapidly evolving, complex series of events, which include intravascular, endothelial, neuronal, glial, and inflammatory changes that either progress to cell death or resolve with the survival of a functioning neuron. Whereas some cells may die immediately, other dysfunctional neurons may survive if interventions to improve perfusion and maintain cell function are prescribed rapidly.

Research advances are providing new insights into a number of cellular phenomena that develop during ischaemia.

The theory of the ischaemic penumbra forms a critical underpinning for the current approach to acute ischaemic stroke. Following arterial occlusion, a core of brain may have an irreversible neuronal injury because of profound hypoperfusion and cell dysfunction. This core of brain tissue rapidly becomes necrotic and unsalvageable. Although the core of completely ischaemic tissue has markedly reduced cerebral blood flow and metabolic activity adjacent, partially ischaemic tissue (penumbra) has borderline levels of blood flow and metabolic function. Fortunately, the area of dysfunctional

but not dead brain tissue may be relatively large in the setting of acute ischaemic stroke. Potentially, the majority of the affected area of the brain may encompass the penumbra. Dysfunctional borderline areas have the potential for recovery with restitution of adequate perfusion or institution of measures to halt the metabolic consequences of ischaemia.

TYPES OF ISCHAEMIC EVENTS

Ischaemic cerebrovacular disease can be divided into subgroups based on the area of brain involved, the time course of the event, and the severity of neurological impairment.

1)Time Course

-Transient ischaemic attack

- Amaurosis fugax

-Cerebral infarction with transient symptoms

-Reversible and partially reversible ischaemic neurological deficits

-Minor ischaemic stroke

-Acute ischaemic stroke

-Completed stroke

-Vascular dementia

2.Area of Brain-Vascular infrastructure

-Vertebral artery

Posterior inferior cerebellar artery

-Basilar artery :

Anterior inferior cerebellar artery

Internal auditory artery

Superior cerebellar artery

-Posterior cerebral artery

-Internal carotid artery :

-Anterior cerebral artery

-Middle cerebral artery

-Cortical branch arteries

-Watershed (borderzone) infarction

-Vascular centrencephalon

-Lacunar infarction [10]

TIA:

The term transient ischaemic attack (TIA) describes a brief episode of transient focal neurological impairment that is of vascular origin. The original definition of TIA included a time limit on neurological symptoms that could extend to 24 hours, but this time window is far too long. Episodes of TIA usually last only a few minutes and almost all resolve within 20 minutes. In fact, most patients whose neurological symptoms persist more than 1 hour have a hypodense lesion found on

CT scan of the brain.

Rather than being a risk factor for stroke, a TIA is a warning sign and a

marker of instability for the underlying disease causing a stroke. The occurrence of a TIA should lead to prompt evaluation and initiation of therapies to prevent stroke.

An episode of painless, transient monocular visual loss, or amaurosis fugax (transient monocular blindness), predicts ischaemic stroke and is a warning for either retinal or cerebral ischemia. Its importance as an omen for stroke derives from the common blood supply (internal carotid artery) to the eye and the ipsilateral cerebral hemisphere. Cerebral infarction with transient symptoms (CITS) is made when a patient clinically has a TIA but a

subsequent brain imaging study demonstrates an infarction. In most cases, these patients will have symptoms that last 1 hour or longer. [11]

Terms such as reversible ischaemic neurological deficit (RIND) and partially reversible ischaemic neurological deficit (PRIND) previously were applied to events that lasted longer than 24 hours or cases in which the neurological signs did not completely disappear [12]. These terms have outlived their usefulness and have been supplanted by the term minor ischaemic stroke. A clinically silent infarction also may be found on brain imaging. These strokes can be detected in up to 20% of patients who are seen with signs of an acute stroke. First few hours or days after onset, the term acute (hyperacute) ischaemic stroke has been coined. The term brain attack is being used to describe stroke to the public.

The upper time limit for acute ischaemic stroke has not been defined, but 24 hours probably is the maximal duration. A better time limit might be the first 3-12 hours. The diagnosis of stroke in evolution (progression stroke) is made when a patient's neurological signs are worsening. A patient whose neurological signs persist for at least 24 hours is considered to have had a completed stroke. Whereas a single stroke causes focal neurological impairments that reflects the area of brain injury, the effects of recurrent strokes are more pervasive. In particular, resulting declines in cognition and intellect lead to vascular dementia.

Vascular dementia can be the result of multiple, bilateral infarctions, particularly in the basal ganglia. Stepwise mental deterioration occurring in conjunction with other neurological signs is the hallmark for a variety of vascular dementia called multi-infarct dementia.

ETIOLOGY:

The causes of cerebral ischaemia and infarction are:

1)Arterial wall disorders

- Atherothoromboembolism
- Intracranial small vessel disease (lipohyalinosis, arteriolosclerosis, microatheroma)
- Trauma
- Dissection
- Fibromuscular dysplasia
- Congenital arterial anomalies
- Moyamoya syndrome
- Embolism from arterial aneurysms

Inflammatory vascular diseases

- Antiphospholipid antibody syndrome
- Primary systemic vasculitis
- Rheumatoid disease

- Sjogren’s syndrome
- Behcet’s disease
- Relapsing polychondritis
- Progressive systemic sclerosis
- Sarcoid angiitis
- Isolated angiitis of the central nervous system
- Malignant atropic papulosis
- Acute posterior multifocal placoid pigment epitheliopathy
- Buerger’s disease
- Leukoaraiosis
- Irradiation

➢ Infections

Embolism from the heart

Paradoxical embolism from the venous system

➢ Atrial septal defect

➢ Ventricular septal defect

➢ Patent foramen ovale

➢ Pulmonary arteriovenous fistula

Left atrium

- Sino atrial disease
- Myxoma
- Inter-atrial septal aneurysm

Mitral valve

- Rheumatic stenosis or regurgitation
- Infective endocarditis
- Non-bacterial thrombotic (marantic) endocarditis
- Prosthetic valve
- Mitral annulus calcification
- Mitral leaflet prolapse
- Libman-Sacks endocarditis
- Papillary fibroelastoma

Left ventricular mural thrombus

- Acute myocardial infarction
- Left ventricular aneurysm
- Cardiomyopathy
- Myxoma
- Blunt chest injury
- Mechanical artifical heart

Aortic valve

- Rheumatic stenosis or regurgitation
- Infective endocarditis
- Non-bacterial thrombotic (marantic) endocarditis
- Prosthetic valve
- Calcification and / or sclerosis
- Syphilis
- Congenital cardiac disorders

Others

- Primary oxalosis
- Hydatid cyst

2) Haematological disorders :

- Polycythemia
- Essential thrombocythaemia
- Sickle-cell disease / trait and other haemoglobinopathies
- Iron deficiency anaemia
- Paraproteinaemias
- Paroxysmal nocturmal haemoglobinuria
- Thrombotic thrombocytopenic purpura
- Disseminated intravascular coagulation
- Thrombophilias and other causes of 'hypercoagulability'

Miscellaneous conditions

- Pregnancy / puerperium
- Oral contraceptives and other female sex hormones
- Drug abuse
- Cancer
- Perioperative
- Migraine
- Inflammatory bowel disease
- Homocystinaemia
- Fabry's disease
- Mitochondrial cytopathy
- Hypoglycemia
- Fibrocartilaginous embolism
- Snake bite
- Fat embolism
- Epidermal naevus syndrome
- Susac's syndrome
- Nephrotic syndrome
- CADASIL (Cerebral Autosomal dominant arteriopathy with subcortical

CLINICAL FEATURES OF ISCHAEMI STROKE

MCA STROKE(middle cerebral artery stroke):

Focal symptomes of infarction in middle cerebral artery :

1. Motor disorders – Hemiplegia

2. Sensory disorders - Hemianesthesia

3. Gaze paresis

4. Visual disorders – Hemianopia

The lesion of the left MCA:

1. Aphasia

2. Alexia

3. Acalculia

The lesion of the right MCA.

Apracto – agnostic syndrome

- Anozognosia
- Astereognosis
- Autotopognosia
- Apraxia

Focal symptomes of infarction in anterior cerebral artery :

- Spastic hemiparesis with the prevalence in proximal part of upper extremity and distal part of lower extremity
- Symptoms of oral automatism
- Psychiatric disorders – frontal mental disorders
- Dysphagia
- Dysphonia
- Astasia, abasia
- Motor aphasia
- Retention of urine [13]

Focal symptomes of infarction in posterior cerebral artery :

- Hemianopsia
- Visual agnosia
- Hemianesthesia
- Hyperpathia
- Desorientation in space and time [14]

Focal symptoms of infarction in vertebral artery:

Atherosclerosis has a predilection for the origin and distal segments of these vessels, predictably atheromatous disease at each site produces is own clinical syndrome. Atherothrombotic lesion have a predilection for first and fourth segments of the vertebral arteries but narrowing of first division rarely produce stroke because of collaterals. Fourth segment occlusion produces Wallenburg's syndrome (lateral medullary syndrome) [15].

In case of extracranial lesion:

- systemic dizziness
- Hearing disorders
- Visual disorders
- eye movements disorders
- Vestibular and equilibrium disorders
- paresis with sensory disturbances in extremities
- some patients have " drop- attacks ".

Focal symptoms of infarction in basilar artery:

- loss of consciousness
- eye movements disorders

- pseudobulbar syndrome [16]

Anterior choroidal artery occlusion presents with :

The complete clinical syndrome of anterior choroidal artery occlusion consists of :

• Contralateral hemiplegia.

• Contralateral hemianesthesia

• Homonymous hemianopia [17]

However, because this territory is also supplied by penetrating vessels of proximal MCA and the posterior communicating and posterior choroidal arteries, minimal deficits may occur and patient frequently recovers completely.

ICA occlusion presents with :

The clinical picture of ICA occlusion varies can be asymptomatic but usually presents with deficit similar to MCA occlusion. Transient monocular blindness occurs in about 25% patients.

Patients with fetal posterior cerebral artery may present with symptoms referable to peripheral territory. Carotid artery bruit is an important sign and a high pitched prolonged carotid bruit fading into diastole is often associated with highly stenotic lesions [18].

Anterior inferior cerebellar artery presents with :

Ipsilateral deafness, facial weakness, vertigo, nausea, vomiting, nystagmus, tinnitus, cerebellar ataxia, Horners syndrome, paresis of conjugate gaze. Contralateral loss of pain and temperature [19].

Important syndromes of posterior circulation are:

- Lateral medullary syndrome
- Medial medullary syndrome
- Ventral / dorsal syndrome. These can be present in complete or partial form or in combination. Among these lateral medullary syndrome is more common.

Lateral medullary syndrome

Same side :

- Pain, numbness, impaired sensation over half the face.
- Dysphagia, hoarseness, paralysis of palate.

Opposite side :

- Impaired pain and thermal sensation

Medial medullary syndrome :

On the side of lesion – Paralysis with atrophy of half of the tongue.

On side opposite lesion – Paralysis of arm and leg sparing face, impaired tactile and proprioceptive sensation over half the body [20].

HEMORRHAGIC STROKE:

This is a common cause of stroke and could be de to ruptured av malformation, aneurysmal rupture se of anticoagulant or thrombolytics cerebral amyloidosis.

Primary (Hypertensive) Intracerebral Hemorrhage

In order of frequency the cerebral sites are (1) the putamen ,internal capsule (50percent); (2) temporal, parietal, or frontal lobes ; (3) the thalamus; (4) a cerebellar hemisphere; and (5)the pons. The vessel involved is usually a penetrating artery that originates from a larger trunk vessel. About 2 percent of primary hemorrhages are multiple.

However, a hemorrhage of this type almost never ruptures through the cerebral cortex. When the hemorrhage is small and located at a distance from the ventricles, the CSF may remain clear even on repeated examinations. In the first hours and days following the hemorrhage, a limited amount of edema accumulates around the clot and adds to the mass effect. Hydrocephalus may occur as a result of bleeding into the ventricular

system or from compression of the third ventricle. Extravasated blood undergoes a predictable series of changes [21].

Within a few days, hemoglobin products, mainly hemosiderin and hematoidin, begin to appear Hemorrhages may be described as massive, moderate, small, slit, and petechial. *Massive* refers to hemorrhages several centimeters in diameter; *small* applies to those 1 to 2 cm in diameter and less than 20 mL in volume; a moderate-sized hemorrhage, of course, falls between these two, both in diameter and in volume.

Pathogenesis The hypertensive vascular lesion that leads to arterial rupture in some cases appears to arise from an arterial wall altered by the effects of hypertension, i.e., the change referred to in a preceding section as segmental lipohyalinosis and the false aneurysm (microaneurysm) of Charcot-Bouchard. Ross Russell has affirmed the relationship of these microaneurysms to hypertension and hypertensive hemorrhage and their frequent localization on penetrating small arteries and arterioles of the basal ganglia, thalamus, pons, and subcortical white matter. However, in the few hemorrhages examined in serial sections by our colleague C. M.Fisher, the bleeding could not be traced to Charcot-Bouchard aneurysms.

Takebayashi and coworkers, in an electron microscopic study, found breaks in the elastic lamina at multiple sites, almost always at bifurcations of the

small vessels. Possibly these represent sites of secondary rupture from tearing of small vessels by the expanding hematoma [22].

Clinical Picture brain hemorrhage is a very sudden also from ancient times surrounded by “an aura of mystery and inevitability.” It has been given its own name, “apoplexy.” The prototype is an obese, plethoric, hypertensive male who, while sane and sound, falls senseless to the ground—impervious to shouts, shaking, and pinching— breathes stertorously, and dies in a few hours. A massive blood clot escapes from the brain as it is removed postmortem.

Several general features of intracerebral hemorrhage should be emphasized. *Acute reactive hypertension*, far exceeding the patient’s chronic hypertensive level, is a feature that should always suggest hemorrhage; it is seen with moderate and large clots situated in deep regions. *Vomiting* at the onset of intracerebral hemorrhage occurs much more frequently than with infarction andshould always suggest bleeding as the cause of an acute hemiparesis.

Severe headache is generally considered to be an accompaniment of intracerebral hemorrhage and in many cases it is, but inalmost 50 percent of our cases headache has been absent or mild in degree. *Nuchal rigidity* is found frequently; but again, it is so often absent or mild that failure to find it should does not eliminate the diagnosis. (Stiffness of the neck characteristically disappears as coma deepens). It should also be noted that

the patient is often alert and responding accurately when first seen. This can be true even when the CSF is grossly bloody; thus the adage that hemorrhage into the ventricular system always precipitates coma is quite incorrect. Only if bleeding into the ventricles is massive will coma result.

The fundi often show hypertensive changes in the arterioles. Rarely, white-centered retinal hemorrhages (Roth spots) or fresh preretinal (subhyaloid) hemorrhages occur; the latter are much more common with ruptured aneurysm, arteriovenous malformation, or severe trauma. *Headache, acute hypertension,* and *vomiting* with a focal neurologic deficit are therefore the cardinal features and serve most dependably to distinguish hemorrhage from ischemic stroke.

Hemorrhages that complicate the administration of anticoagulants, like those from some vascular malformations, may evolve at a slower pace. Usually there are no warnings or prodromal symptoms; headache, dizziness, epistaxis, orother symptoms do not occur with any consistency. There is no age predilection except that the average age of occurrence is lower than in thrombotic infarction, and neither sex is more disposed.

The incidence of hypertensive cerebral hemorrhage is higher in African Americans than in whites and seems recently to have been reported with increasing frequency in Japanese. In the majority of cases, the hemorrhage has its onset while the patient is up and active; onset during sleep is a rarity.

There has long been a notion that acute hypertension precipitates the hemorrhage in some cases. This is based on the occurrence of apoplexy at moments of extreme fright or anger or intense excitement, presumably as the blood pressure rises abruptly beyond its chronically elevated level. The same has been described in relation to taking sympathomimetic medications such as phenylpropanolamine (Kernan et al), ephedra, or cocaine and to numerous other similar circumstances. However, in fully 90 percent of instances, the hemorrhage occurs when the patient is calm and unstressed (Caplan, 1993). The level of blood pressure rises early in the course of the hemorrhage, but the preceding chronic hypertension is usually of the "essential" type. Other causes of hypertension must always be considered—renal disease, renal artery stenosis, toxemia of pregnancy, pheochromocytoma, aldosteronism, adrenocorticotropic hormone or corticosteroid excess and, of course, sympathetically active drugs.

There is ordinarily only one episode of hypertensive hemorrhage; recurrent bleeding from the same site, as happens with saccular aneurysm and arteriovenous malformation, is infrequent. However, it is now recognized by serial CT scanning that in many instances, as the patient's condition worsens over a few hours, there may be slight enlargement of the hematoma. In the series of Brott and colleagues, one-quarter of hematomas were found to have enlarged in the first hour and another 12 percent in the

first day. Blood that has extravasated into cerebral tissue is absorbed slowly, over a period of months, during which time symptoms and signs recede. Hence the neurologic deficit is never transitory in intracerebral hemorrhage, as it so often is in embolism; for the same reason, one does not expect rapid improvement in the neurologic deficit from one examination to another.

CORTICAL VENOUS THROMBOSIS:

Cerebral venous thrombosis, including venous sinus thrombosis and cortical vein thrombosis, is a relatively rare cause of stroke. The annual incidence is estimated to be 3- 7 cases per million people representing <1% of all strokes It is more common among young women and children. Though it can cause devastating injury to the brain, most patients have a good prognosis if it is recognized and treated early.

PATHOPHYSIOLOGY

Multiple causative factors are associated with the development of cerebral venous thrombosis . Thrombosis develops from common pathways of hypercoagulability, hemoconcentration, direct injury or inflammation of the vessel, venous stasis, and obstruction of flow. Two specific mechanisms are responsible for the etiology of injury. Thrombosis in the cortical veins causes localized vasogenic edema, venous infarction with cytotoxic edema, and hemorrhage. Thrombosis of the large venous sinuses obstructs venous

drainage leading to impaired CSF absorption through the arachnoid villi and intracranial hypertension withouthydrocephalus [23].

CLINICAL FEATURES

The onset of symptoms can be acute, subacute or chronic. Headache is the most common presenting symptom of cerebral venous thrombosis, present in nearly 90% of patients. Other common presenting symptoms include focal or generalized seizure (40%), focal motor weakness (37%), encephalopathy or change in mental status (22%), vision loss (13%), diplopia (13%), stupor or coma (13%). The particular constellation of symptoms and exam findings reflects the extent to which the cortical veins (seizure and focal neurologic symptoms) and large venous sinuses (elevated intracranial pressure, bi-hemispheric symptoms) are involved.

Papilledema may be present in 25-30% of patients. Thrombosis of the deep cerebral veins (vein of Galen, straight sinus, internal cerebral veins) can produce a spectrum from mild cognitive disturbances to coma. Thrombosis of the cavernous sinus produces a characteristic syndrome of orbital pain, proptosis, chemosis and variable dysfunction of cranial nerves III, IV, V, and VI [24].

YOUNG STROKE

Cerebrovascular atherosclerosis was assumed to be the cause of Cerebral nfarction if artiography revealed any type or degree of plaque in the appropriate proximal arteries and if other probable causes were absent. Although arteriographically visible, asymptomatic cerebrovascular atherosclerosis is relatively uncommon in people under 40, it is possible that some patients had asymptomatic plaques and Cerebral infarction of other etiology [25.]

Incidence of Young Stroke

Below age group of thirty five , rates are less than ten in hundred thousand .and in the age group 33 to 42 , it is about twent two to forty five in hundred thousand patients [26].

ETIOLOGY OF YOUNG STROKE:

Majority of strokes are due to SAH and ICH in young people (40–55%) on comparing to the whole poplation of stroke (15–20%), cerebral infarction is very common. High incidence of cerebral infarction was found in young people with usual vascular risk factors is seen, especially in countries which are developing due to more population is involved in smoking and industrialization. However, etiology of stroke in

young people differ in frequency compared to those observed in the elderly. This is especially true in adult patients who are below 30 years of age [27].

CARDIOEMBOLIC STROKE

Mitral valve disease, which is an etiology for cardioembolic stroke in young people , is more often seen in patient poplation having rheumatic heart disease as an etiology [28].

Patent Foramen Ovale (PFO) and Stroke :

A relation which occurs between patent foramen ovale and youn stoke remains a confused topic . PFO is seen among young patients who are diagnosed with cryptogenic stroke [45] .

Thrombophilia and Stroke: Apart from APLAS, thrombophilia itself is not an etological risk factor for stroke , and there are few evidences showing that mutation in prothrombin gene, in particular, increases the risk of ischaemic stroke in patients with PFO [46].

Migraine and Stroke

Studies show migraine, specifically migraine with auera, there is more chances of stroke in women who are under 45 years of age . The mechanism still not clear.

Stroke in the Puerperium

Incidence is around 4 to 210 in 100 000 deliveries , causing to atleast 12% of maternity deaths. Cerebral haemorrhage was found to be an important etiology of death in patients with eclampsia but some studies shows preeclampsia also there is ischaemic stroke are. Subarachnoid haemorrhage is 3rd important etiology for for nonobstetric-related maternal death, which is most often de to aneurysmal rupture [29].

Antiphospholipid Antibody Syndrome

Ischaemic stroke is found in antiphospholipid syndrome according to a large cohort study . presence of lupus anticoagulant has an increased risk compared to other antiphospholipid antibodies is still unclear . links have been found between young ischaemic stroke , lupus protein .both of these were assoiated .anticardiolipin antibodies [30].

Nonatherosclerotic Vasculopathies

The most common cause for non atherosclerotic vasculopathy is cervical artery dissection. Next is vasulitis arising as a result of infection ,next are moyomoya which is seen more in asian population and the migrane bt the contribute less than 1 percent. These patients show geographical and sometime ethical variation like moyamoya takayasu was also fond to be more common in asian population.

Vasulitis due to infectious cause is found more in young stroke patients of asian origin . with the exclusion of cerebral angitis systemic vasculitis only rarel causes stroke. But concurrent atherosclerotic disease may increase the stroke predisposition in such patients .

Extracranial ArterialDissection:

Cervical artey dissection is a significant cause of stroke in middle aged men but the exact etiolog remains unrecognised.trauma, infections and even migrane have been linked to CAD but there is lack of strong evidence to support it.

Haemorrhagic Stroke

Many studies tell that subarachnoid and intracranial haemorrhage are the etiological factors in around 25–55% of stroke patients who are within the age of 45 with incidence around 2 to 5 . The usual link which is

between hypertension and intracranial haemorrhage may be the reason why ther is more cases of intracranial haemorrhage seen in young blacks of America, with one study showing there is more cases of hypertensive intracranial haemorrhage seen in young blacks. A reasonably more cases of intracranial haemorrhage was seen in in young Nigerians [47]

HYPERHOMOCYSTEINEMIA:

Man observational studies have been done to establish a positive correleation between serum homocysteine and stroke and the results had a positive relation between the two.

Homocsteine levels has to bemeasured in any stroke patients of younger age group and in whom definite etiolog could not be established .

They are supplemented with folate ,vitamin B12 and vitamin B6.

CRYPTOGENIC STROKE

In about 30% of patients, the cause of stroke cannot be identified despite the detailed and comprehensive aetiological work up described in this Review. Some of these patients might have classic vascular risk factors, but they do not show evidence of large atherosclerotic or smallvessel arterial disease. Minor atherosclerotic lesions might be missed by current diagnostic and imaging techniques.

A frequent mistake is the diagnosis of cryptogenic stroke in patients with incomplete or delayed aetiological investigation. This misdiagnosis is of particular importance in dissection, which can resolve quickly, and in intracardiac thrombus, which can either resolve or fragment and embolise. Results of some biological diagnostic tests (eg, antiphospholipid antibodies for antiphospholipid syndrome or platelet count for thrombocythaemia) can fl uctuate, and therefore repeated assessment is needed. Repeated or extended Holter monitoring might be necessary if paroxysmal arrhythmias are suspected. Repeated angiography might also be necessary to distinguish between reversible cerebral vasoconstriction syndrome, in which the various segmental arterial narrowings are reversible, and vasculitis, atherosclerosis, or other vasculopathies of intracranial arteries, in which the narrowings persist or even progress [31].

NEW RISK FACTORS FOR STROKE:

Inherited Susceptibility

A history of stroke in family is one of the risks for stroke of ischaemic etiology, but the pathogenesis is very unclear . Inheritence of risk to ischemic stroke can be due to direct presence of a particular single gene, various interactions of a gene with environmental factors, or an combined effect of several genes (a gene-dose effect), or mutual co effects of various genes. A classic mendelian type of inheritance of single-gene disorder is

very uncommon , causing for less than one percent of cases of ischemic stroke.

Inflammatory Markers:

Leukocyte and Monocyte Counts

Monocyte count was found to be an predictor of future carotid artery atherosclerosis in patients without any carotid atherosclerosis.

High-Sensitivity C-Reactive Protein

Man studies have demonstrate that highly-sensitive C-reactive protein is a predictor of stroke, MI, and vascular death in healthy patients .

Hemostatic Factors: Fibrinogen

The relation between increased levels of fibrinogen and risk of vascular (and also acute coronery events) was linar.

Microalbuminuria

The microalbuminuria , been found to be increasingly associated with stroke ,mi and other vascular events.

Cystatin C

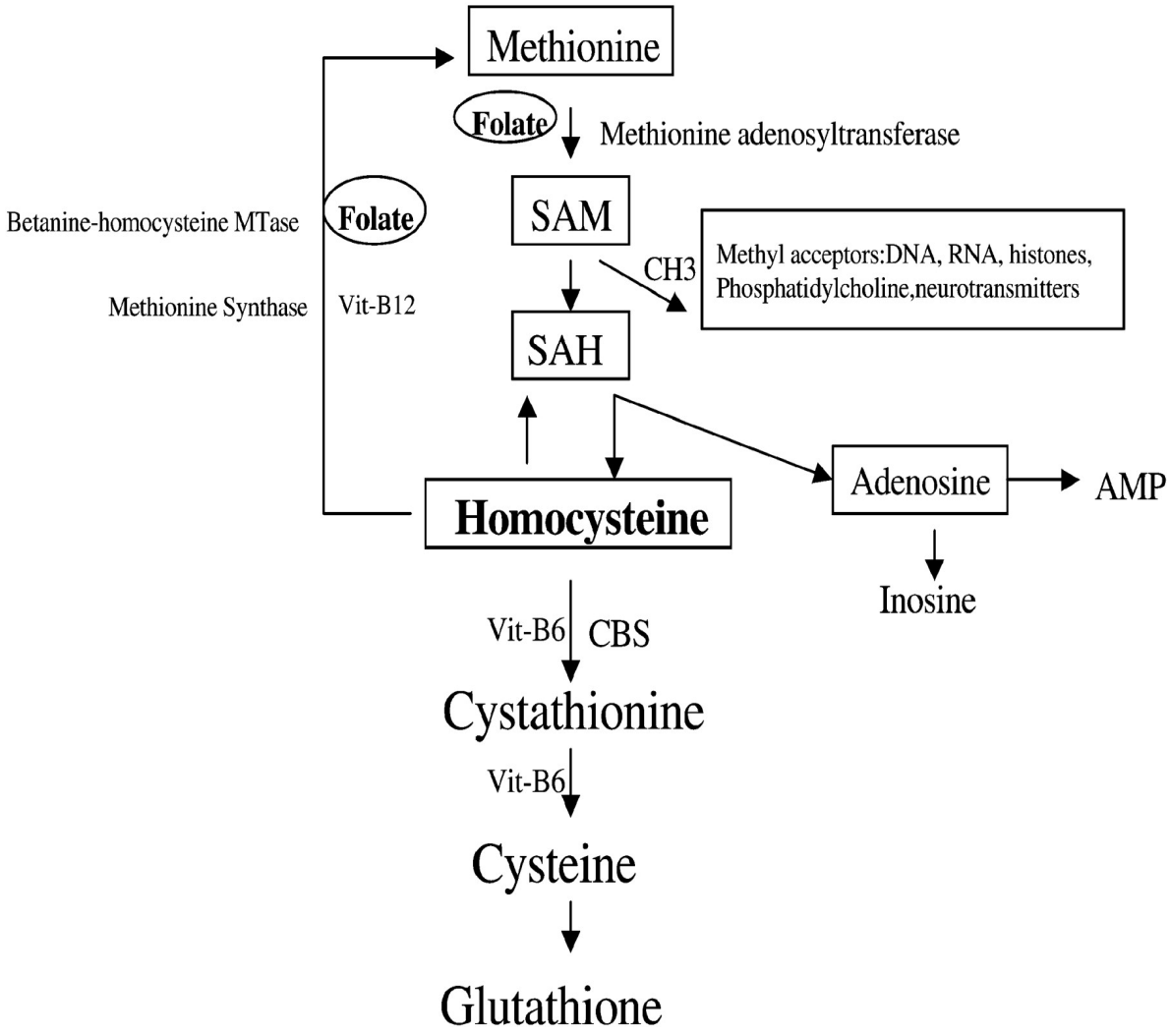
Cystatin C which is measurement of renal function was to be associated with age, powerful of risk of stroke, MI, and death from vascular causes in elderly and in some patients irrespective creatinine [48].

HYPERHOMOCYSTEINEMIA AND STROKE:

HOMOCYSTEINE:

Homocysteine (2-amino-4-mercapto butyric acid) is a sulfur-containing amino acid from a nonprotein source; it is not included in the structure of any protein and is synthesized from methionine. Homocysteine is oxidized rapidly in plasma and thus it can be found in many forms.

Figure 3 HOMOCYSTEINE METABOLISM



Most of it is bound to albumin with a disulfide bond. The rest is in unbound free disulfide and sulfhydryl forms. Homocysteine exists at the junction point of 2 important pathways and is regulated by many different enzymes. The destiny of homocysteine, between de novo methionine biosynthesis and the transsulfuration pathway, is determined by S-adenosylmethionine (SAM) allosterically

In the homocysteine remethylation cycle, at the beginning, 5,10-methylene-THF is reduced to 5-MTHF by 5,10-methylene tetrahydrofolate reductase (MTHFR).

This is a unique in vivo reaction that produces 5-MTHF. Vitamin B12-dependent methionine synthase then converts the homocysteine into methionine; in this process, 5-MTHF is transformed into THF. This final step requires methionine synthase reductase (MSR), which activates the methionine synthase by reducing it. In addition, homocysteine can be converted into methionine by betaine-homocysteine methyltransferase (BHMT), which is not dependent on vitamin B12. Subsequently, synthesized methionine is transformed into SAM, which is a general methyl donor for some important biomolecules, such as adrenaline, phosphatidylcholine, and carnitine, by methionine adenosyl transferase and ATP. The cycle is then completed with the transformation of SAM into S-adenosyl homocysteine (SAH), and later, back into homocystein E.

HYPERHOMOCYSTENEMIA AND DISEASES:

Normal fasting plasma homoysteine is from five to fifteen micro mol .

Hyperhomocysteinemia is further classified as :

Mild -15-30

Moderate - 30- 100

Severe - > 100

PATHOGENESIS OF HYPERHOMOCYSTENEMIA:

EFFECT ON ENDOTHELIAL CELLS:

- 1it causes oxidation damage to vessels
- 2 decreases vascular relaxation
- 3causes coagulation abnormality
- Other possible mechanisms are:

a) increased homocysteine releases oxidative free radicals which agments the atherosclerotic process.

b) chronic diseases sometimes causes elevation of homocysteine due to some immune activation [33]

FACTORS AFFECTING SERM HOMOCYSTEINE LEVEL:

It can be inherited or acquired

INHERITED CAUSES:

Primary hyperhomocystenemia

Due to inherent deficienc of the enzymes involved inhe homocysteine metabolism.

Cystathione beta synthase deficiency

It is inherited as an autosomal recessive disorder .it is the commonest type of deficiency and is characterized by skeletal deformation ,mental retardation,lens dislocation and premature atherosclerosis.

5,10 methylene tetra hydro folate reductase deficiency

This is common in european with a prevalence of about 12% .more prevalent in mediteranean region. This is due to mutatons in MTHFR gene mutations C677T results in alanine valine substitution .it results in increased homocysteine level especially in the presence of low plasma folta level .another mutation in the MTHFR gene , A1298C resulting n glutamic acid to alanine substitution is also identified.but

the influence of this mtatiion in plasma homocystene levelis not clearly described till now [49].

ACQUIRED CAUSES:

Physiological

Tobacco use

Coffee consumption

Vitamin deficiency like vitamin B2, B6,B12,folate

Systemic disorders-

Liver disease

Renal disease

Diabetes mellitus

Pernicious anema

Sle

Hypothyroidism

Psoriasis

ALL

Organ transplantation

Malignancy of ovary ,breast

Drugs- nicotine ,metformin , thiazide, nicotinic acid, folate antagonist, vitamin B6 antagonist like oral contraceptives etc.

Age and gender:

In both men and women plasma homocysteine level increases with age .This age related changes ma be due to difference intake of nutrients like vitamin B6,B12 etc. premenopasal women the plasma homocysteine level is lower compared to men of same age .post menopausal women have higher plasma level compared to pre menopausal women .this may be due to influence of sex steroids.

Nutritional intake:

Nutritional factors like decreased intake of vitamin B6,B 12,folate result in increasd homocysteine levels.This is important in strict vegetarians because vegetarian diet is usually low in vitamin B6 ,B 12.so individuals following vegetarian diet serum homocysteine level is found to be elevated

Life style fators:

Physical activity lowers homocystein level .increased caffeine intake and smoking causes increase in homocysteine level. Alcohol has variable effect on homocysteine level where as excessive intake results in increase plasma homocysteine level. This is attributed to changes in one carbon metabolism in excessive alcohol intake and also to deficiency of B-complex vitamins in chronic alcoholics.

Liver disease

Liver plays an important role in the synthesis and metabolism of homocysteine .in chronic liver disease there is increase in plasma homocysteine level. This is due to decreased availability and utilization of B complex vitamins and also decreased expression of genes involved in homocysteine metabolism in diseased liver [50].

Renal disease

In patients with impaired renal function the levels of homocysteine and other sulphur containing amino acids will be increased. This is due to impaired excretion of homocysteine by diseased kidney and also there is impairment of extra renal metabolism of homocysteine [34].

Diabetes mellitus

In diabetic individuals onset of vascular disease is associated with increase homocysteine level, also insulin resistance is associated with increased homocystein level. Hyperhomoysteinemia increases the risk of vascular diseases in diabetics.

Renal transplantation.

Immunosupression used after renal transplantation like cyclosporine also plays an important role in increasing plasma homocysteine level .

Homocsteine and malignancy:

Elevated homocysteine levels can be seen in various malignancy .it is more evident in patients with cancer of the breast ,ovary, colon ,prostate. This was demonstrated by james WU. He demonstrated that elevated homocysteine levels in these patients correlates with the level of tumor markers and decline with tumor regression during treatment.

Complications of hyperhomocysteinemia

1.Ischaemic Heart Disease

2. Cerebrovasclar Disease

3.Venous Thromboembolism

4. Central retinal artery occlusion

5. Pre eclampsia

6. Peripheral vascular diseases

7. Hypertension

8. Diabetes Vascular Complications [35]

Homocysteine and hypertension

In 1969, McCully recognized the elevation in the concentration of plasma homocysteine can lead to an increased risk of cardiovascular disease.

PATHOGENESIS OF HOMOCYSTEINE:

It is now widely accepted that increased plasma homocysteine (Hcy) is associated with increased cardiovascular risk, independently of other atherosclerosis risk factors. From a pathophysiologic point of view, homocysteinaemia is associated with

1) Increased thrombogenicity,
2) Increased oxidative stress status, over activation of redox-sensitive inflammatory pathways
3) Impaired endothelial function,4 and
4) finally atherogenesis.

HOMOCYSTEINE AS A RISK FACTOR FOR ATHEROSCLEROSIS:

The role of homocysteine in atherosclerosis has been well elucidated. All the large meta-analyses conducted during the last decade yield consistent. homocysteine can be considered as an independent risk factor for cardiovascular disease (CVD). The first large meta-analysis published in 1995 pointed out that homocysteine is strongly associated with vascular disease, arguing that an increment in total homocysteine by 5 mmol/L

Is equivalent to the elevation in CAD risk induced by a 20 mg/dL increase in plasma cholesterol. Furthermore, it was suggested that Hcy accounts for up to 10% of the population's CAD risk.

Homocysteine and endothelial function

Increasing evidence suggests that homocysteine may increase cardiovascular risk as a result of its detrimental effect on endothelial function. In subjects with homocystinuria, a significant impairment of endothelium-dependent dilation (EDD) has been well documented, while homocysteine has been associated with impaired coronary microvascular dilator function in healthy individuals. Nevertheless, evidence is conflicting in mild homocysteinaemia. Not all observational studies have reported a statistically significant correlation between plasma Hcy and flow-mediated dilation of the brachial artery.

HOMOCYSTEINE AND ENDOTHELIAL NITRIC OXIDE SYNTHASE REGULATION

The close association of Hcy with endothelial dysfunction is largely dependent on its impact on. The uncoupled form of eNOS is a major source of superoxide radicals instead of nitric oxide, in the vascular wall. A decreased supply of endothelial substrate L-arginine, observed in

homocysteinaemia, has been demonstrated to induce endothelial nitric oxide synthase uncoupling in cell cultures of endothelial cells.

HOMOCYSTEINE AND THROMBOTIC MECHANISMS

The link between homocystinemia and vascular thrombosis is now well established. Severe homocysteinaemia accompanying the genetic defects of homocystinuria is closely linked with recurrent vascular thrombosis. Half of the patients with homocystinuria will come up with a vascular event before the age of However, it seems that the homocystinuria-related prothrombotic state mainly concerns veins rather than arteries.

HOMOCYSTEINE-LOWERING TREATMENT AND VASCULAR FUNCTION

Folic acid and vitamins B12 and B6 are essential co-factors in Hcy metabolism.5-MTHF, the circulating form of folic acid, serves as the methyl-donor in the conversion of homocystene to methionine, an enzymatic reaction catalysed by MS. Vitamin B12 is also pivotally implicated in this reaction as it constitutes an essential co-factor of MS, whereas B6 is a co-factor for CBS, the enzyme responsible for the conversion of Hcy to cystathione and finally to cysteine. Therefore, conditions associated with 5-MTHF, B12, or B6 deficiency have been

associated with increased circulating Hcy levels, and these are the first therapeutic targets in the treatment of homocyateinaemia.

Folate administration has been consistently shown to reduce plasma Homocysteine even in healthy individuals without elevated Homocysteine levels. Oral administration of folic acid (0.5–5.0 mg/day) reduces fasting Homocysteine levels by 25–30%, while supplementation with vitamin B12 (0.02–1 mg/day) yields an additional 7% reduction in levels. Vitamin B6 has no effect on fasting Homocysteine levels but significantly lowers post-methionine loading homocysteinaemia.

HOMOCYSTEINE LOWERING AND ENDOTHELIAL FUNCTION

Hcy lowering by folates and vitamins B6 and B12 induce a significant improvement of vascular NO bioavailability and the overall endothelial function by decreasing plasma Hcy, which is a pro-oxidant molecule in human vasculature as we have already discussed. Notably, evidence suggests that folic acid may reverse vascular dysfunction independently of Homocysteine lowering. In a recent double-blind crossover trial, high-dose folic acid (10 mg/day) improved endothelial function in patients post-myocardial infarction, independently of any changes in plasma Homocsteine levels (including total, reduced, or oxidized forms). These findings support our previous observations that folic acid and its circulating metabolite

5-MTHF have direct effects on vascular function in humans, independently of any effects on oxidized or reduced plasma Homocysteine .

Oral folic acid administration(0.4 or 5 mg/day), 7 weeks before scheduled CABG, was combinedwith improved vasomotor responses of the grafts (saphenous veins and internal mammary arteries), reduced vascular superoxide production, and improved endothelial nitric oxide synthase coupling .

HOMOCYSTEINE LOWERING AND BIOCHEMICAL MARKERS OF ENDOTHELIAL FUNCTION AND OXIDATIVE STRESS

Both chronic and acute, experimentally induced, homocysteinaemia are associated with increased oxidative stress and impaired endothelial function in humans. Folate administration in chronic homocysteinaemia is known to reduce pro-thrombotic state, raise antioxidant defensive mechanisms, and lower systemic oxidative stress markers. Concomitant administration of high doses of antioxidant vitamins in the model of experimental, methionine-induced homocysteinaemia prevented the increase of inflammatory markers such as IL-6.[43].

HOMOCYSTEINE-LOWERING TREATMENT AND CLINICAL OUTCOME: ITS ROLE IN PRIMARY AND SECONDARY PREVENTION

The available data for the role of homocysteinaemia in CVD reasonably posed the question of reducing cardiovascular risk through homocysteine lowering therapy-lowering treatment by means of diet folate fortification.Remarkable results were derived from a recently published study that examined the effect of folate fortification of flour in The study showed that folate fortification increased circulating plasma folate levels and reduced plasma homocysteine in the general population.

Importantly, since 1998, when the flour fortification programme with folate (150 mg folate per 100 g flour) became fully mandatory, an accelerated reduction in stroke mortality was observed in North America. In addition, this reduction in mortality was analogous to that predicted by Hcy lowering. However, the same tendency was not observed in Wales and England, where folate fortification was not introduced. Although a causative relationship between Homocysteine, folate, and stroke cannot be deduced from these epidemiological observations, the available data are in favour of the hypothesis that folate fortification contributes to the reduction of stroke mortality, at least at the level of primary prevention.

HOMOCYSTEINE AND CARDIOVASCULAR RISK: FUTURE PERSPECTIVES

It is now widely accepted that, at a cellular level, Homocysteine exerts a detrimental effect on vascular wall and especially on endothelial cells, by decreasing NO bioavailability, increasing intracellular oxidative stress, and by triggering multiple pro-atherogenic mechanisms. In this context, epidemiological studies have clearly demonstrated that plasma homocysteine is an independent risk factor for atherosclerosis. The existing data clearly demonstrate that moderate/ severe homocysteinaemia is associated with thromboembolic events and increased risk for atherothrombosis, and it should be treated with folic acid/B vitamins. However, it is still unclear whether homocysteine -lowering treatment with folic acid/B vitamins has the potential to improve clinical outcome in subjects with mild homocysteinaemia, and the debate on whether Homocysteine lowering treatment with folate has a role in primary or secondary prevention in subjects with plasma Hcy within the normal range is still unresolved [44].

Hyperhomocystenemia and stroke:

In a study conducted by Venkata Madhav , Anjaneya Prasad Pradeep Babu KV in tamil nadu .Homocystene levels were found to be significantly higher in cerebral ischemic stroke patients by 41.8%.

71.7% of cerebral ischemic stroke patients belong to 41 – 60 years age group. Male to female ratio were found to be 1.66: 1.high incidence of hyperhomocystenemia in 56.25% of cerebral ischemic stroke patients without risk factors than patients with hypertension, diabetes, dyslipidemia and smoking associated incidence of hyperhomocystenemia in 34.4% of cerebral ischemic stroke patients. Elevated serum homocysteine is a strong and modifiable risk factor of cerebral ischemic strokes. Many studies are showed the significance of development of complications like cardiac and cerebral vascular events. We support the consideration of serum homocysteine as a regular and routine screening marker to protect target organ damage [36].

MANAGEMENT OF STROKE:

INVESTAGATIONS:

1. **CONFIRM THE DIAGNOSIS**

Computerised tomography (CT scan)

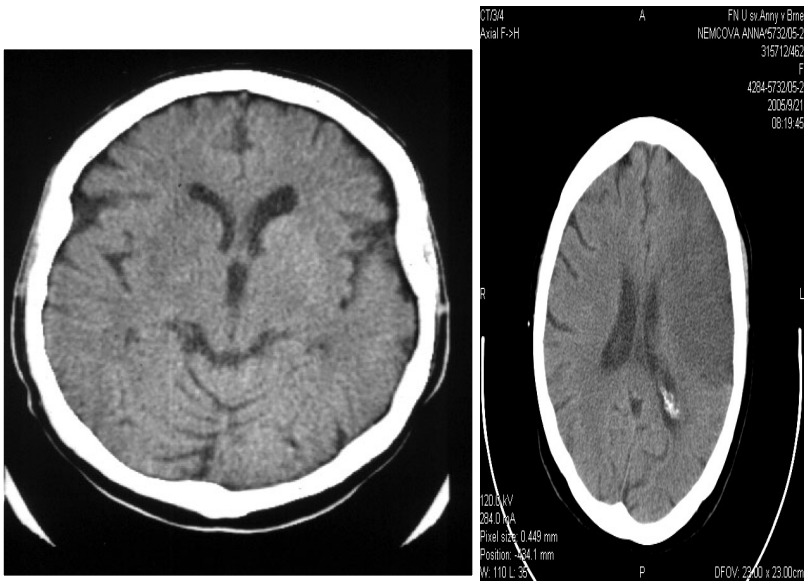
All patients should have a CT scan, urgently if

- conscious level depressed
- diagnosis uncertain
- on anticoagulants

- before commencing/resuming anthitrombotics
- if thrombolysis is considered

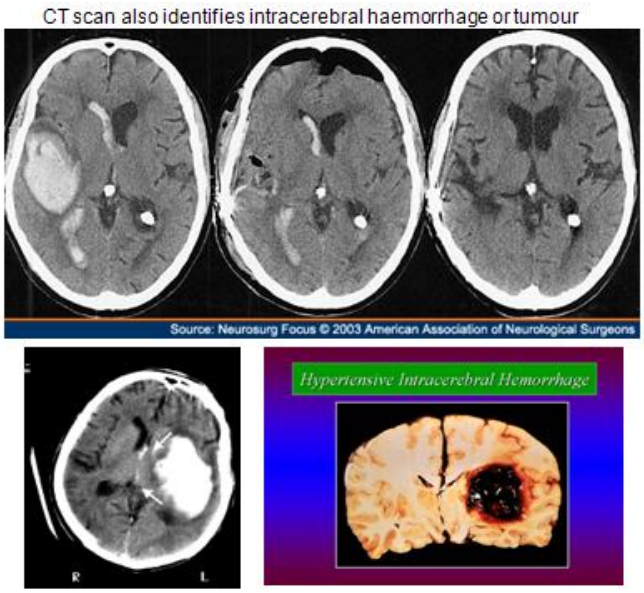
Infarction is evident as a low density lesion which conforms to a vascular teritory. Subtle changes occur within 3 hours in some pts; most scans become abnormal within 48 hours.

Figure 4 CT BRAIN SHOWING INFARCT



CT BRAIN SHOWING HEMORHAGE

Figure 5

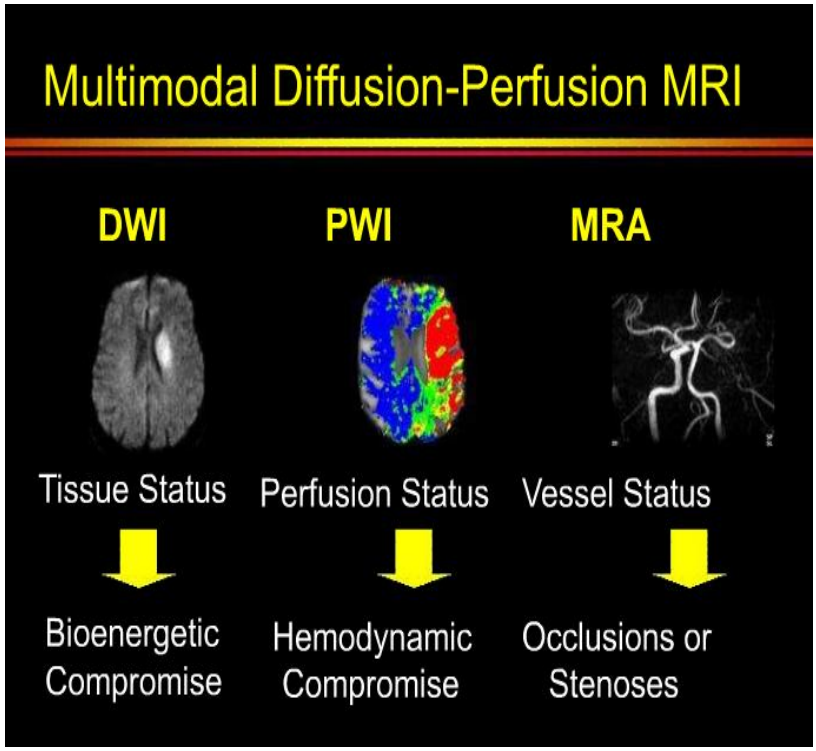


Magnetic resonance imaging: T2 prolongation (hyperintensity in relation to white and grey matter) occurs within hours of onset of ischemic symptoms.

Advanced technique, diffusion weighted imaging (DWI) and perfusion imaging (PWI) show respectively early infarction (cytotoxic oedema) and ischaemic tissue at risk (‘ischaemic penumbra’).

These advanced techniques are valuable predictors of outcome and guide treatments directed as thrombolysis.

Figure 6 MULTIMODAL DIFFUSION –PERFUSION MRI

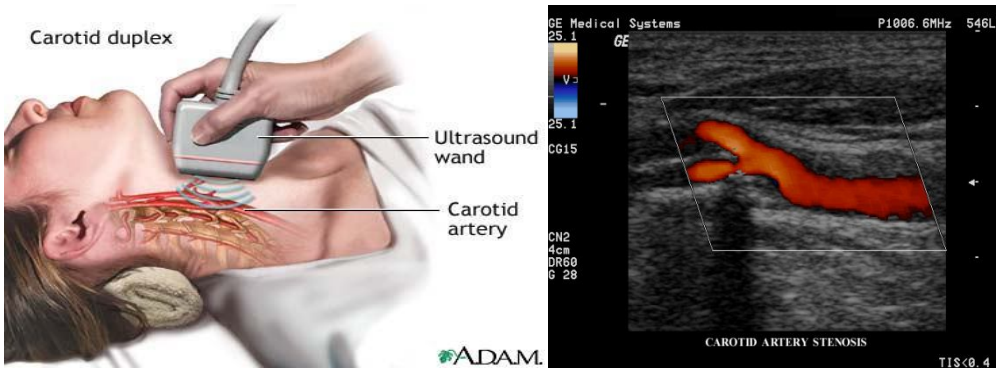


DEMONSTRATE THE SITE OF PRIMARY LESION

a) <u>Non-invasive investigation</u>

Ultrasound – Doppler/Duplex scanning: assesses extra- and intracranial vessels.

Figure 7 CARTID DUPLE



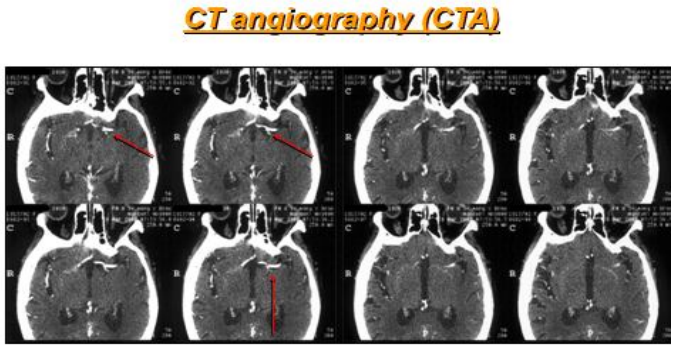
DEMONSTRATE THE SITE OF PRIMARY LESION

a) Non-invasive investigation

Computed tomographic angiography (CTA) – dynamic helical CT, following bolus injection of non-ionic contrast, can be used to investigate both intracranial and extracranial vasculature.

CTA compared with DSA correctly classifies the degree of carotid stenosis in 96% of cases but is insensitive to ulcerative plaques.It is best used in conjunction with Doppler.

Figure 8 CT ANGIO



DEMONSTRATE THE SITE OF PRIMARY LESION

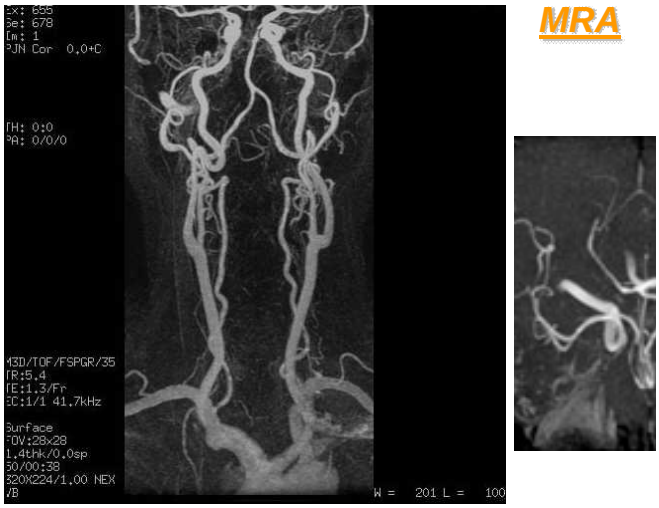
a) Non-invasive investigation

Magnetic resonance angiography (MRA) – 'Time of flight' or contrast enhanced techniques are used. It tends to overestimate the

severity of stenosis. When assessing the carotid arteries it is best used in combination with Doppler.

Its non-invasive nature makes it helpful in investigating the intracranial circulation.

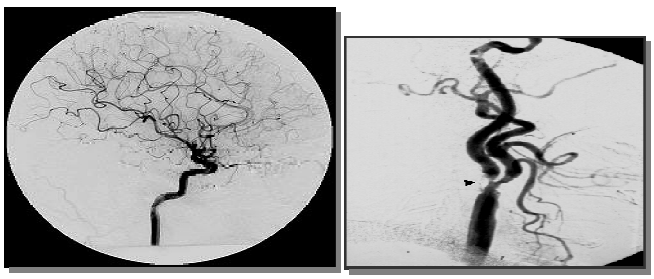
Figure 9 MR ANGIOGRAM



DEMONSTRATE THE SITE OF PRIMARY LESION

b) Digital intravenous subtraction angiography (DSA)

Figure 10



IDENTIFY FACTORS WHICH MAY INFLUENCE TREATMENT AND OUTCOME

- General investigation
- Chest X-ray (cardiac enlargement, HT,…)
- ECG (cardiac disease)
- Blood glucose (diabetes)
- Serum lipids and cholesterol (hyperlipidemia)
- Full blood count (polycythaemia, thrombocytopenia)
- Urine analysis (polyarteritis, thrombocytopenia)
- Auto-antibodies
- Prothrombin time and partial thromboplastin time (PTT)
- Note drug history (oral contraceptives, amphetamines,…)
- Selectively cardiac ultrasound, HIV screen, viscosity studies, anticardiolipin antibodies,
- Serm homoysteine

TREATMENT:

Therapies for stroke prevention and management are designed to (1) prevent first stroke (primary prevention), (2) optimize functional recovery following stroke, and (3) avert stroke recurrences (secondary prevention). Specific measures for treatment and prevention depend upon the patient's

risk factors and stroke mechanism. Diagnostic evaluation of the stroke patient is therefore the key to determination of optimal therapy.

PRIMARY PREVENTION OF STROKE

Randomized trials have demonstrated the benefits of specific interventions to prevent a first stroke among patients with stroke-risk factors (Table 46.1). Treatment of hypertension, for example, is associated with up to a 45% reduction in the risk of stroke.

ACUTE ISCHAEMIC STROKE:

Attention is directed toward preventing the common complications of bedridden patients—infections (pneumonia, urinary, and skin) and deep venous thrombosis (DVT) with pulmonary embolism. Many physicians use pneumatic compression stockings to prevent DVT; subcutaneous heparin.

Water restriction and IV mannitol may be used to raise the serum osmolarity, but hypovolemia should be avoided as this may contribute to hypotension and worsening infarction. Combined analysis of three randomized European trials of hemicraniectomy (craniotomy and temporary removal of part of the skull) shows that hemicraniectomy markedly reduces mortality, and the clinical outcomes of survivors are acceptable [37].

INTRAVENOUS THROMBOLYSIS:

In a study rtPA was given to stroke patients presenting within three hours and it was compared with placebo. Stroke patients treated with rtpa had a better outcome compared to placebo group.

RECOMBINANT TISSSUE PLASMINOGEN ACTIVATOR IN STROKE

Indications :

Clinical diagnosis of stroke

Within three hours from symptom onset to drug administration

CT scan showing without an bleed or

Age >18 years

Consent obtained from the patient.

<u>Contraindications</u>:

1.elevated blood pressure more than 185 systolic and 110 diastolic despite treatment

2.Platelets less than hundred thousand ;hematocrit less than twenty five percent ;

3.when heparin is used within two days.

4.symptoms which has improved very fast.

5.history of head injury within 3 months

6.major surger within fourteen days

7.less severe stroke symptoms

8.GI hemorrhage within twenty one days.

9.Recent MI

10 .Coma , stupor [38]

ENDOVASCULAR TECHNIQUES:

Ischemic stroke from large-vessel intracranial occlusion results in high rates of mortality and morbidity. Occlusions in such large vessels [middle cerebral artery (MCA), internal carotid artery, and the basilar artery] generally involve a large clot volume and often fail to open with IV rtPA alone [39].

ANTITHROMBOTIC TREATMENT:

ASPIRIN:

; there are several antiplatelet agents proven for the secondary prevention of stroke .and aspirin is the approved drug so far [40] .

ANTICOAGULATION:

Numerous clinical trials have failed to demonstrate any benefit of anticoagulation in the primary treatment of atherothrombotic cerebral ischemia. Use of SC unfractionated heparin versus aspirin was tested in IST. Heparin given SC afforded no additional benefit over aspirin and increased bleeding rates. Several trials of LMWHs have also shown no consistent benefit in AIS. Furthermore, trials generally have shown an excess risk of brain and systemic hemorrhage with acute anticoagulation.

NEUROPROTECTION:

Neroprotection has been found to enhance brain s capacity to withstand ischaemia.It acts by actively blocking brains excitatory amino acid s and was proved in animal models. Human studies were not promising. Hypothermia was found to have a good outcome in cardiac arrest patients but not in CVA [41].

REHABILITATION:

Proper rehabilitation may redce mortalit and morbidity due to stroke . Stroke teams must be working round the clock in managing patients with stroke .

The goal of rehabilitation is to make the patient recover from deficit by physiotherapy and return home with minimal deficit. This finding suggests that the human nervous system is more adaptable than originally thought and has stimulated active research into physical and pharmacologic strategies that can enhance long-term neural recovery [42].

HEMORHAGIC STROKE :

Emergency management:

Close attention should be paid to airway management since a reduction in the level of consciousness is common and often progressive. The initial blood pressure should be maintained until the results of the CT scan are reviewed.

Intra cerebral bleed:

Nearly 50% of patients with a hypertensive ICH die, but others have a good to complete recovery if they survive the initial hemorrhage. The ICH scoring system is a validated metric that is useful for prediction of mortality

and clinical outcomes. Any identified coagulopathy should be reversed as soon as possible. For patients taking VKAs, rapid reversal of coagulopathy can be achieved by infusing prothrombin complex concentrates which can be administered quickly, followed by fresh-frozen plasma and vitamin K.

TREATMENT HYPERHOMOCYSTENEMIA IN YOUNG STROKE:

Sinc homocysteine depends on folic acid and vitamin b twelve for its metabolic pathway supplementation of these two vitamins could actually redce the event of stroke and recurrent stroke.

But Some studies showed that suplementaion of vitamin did not decrease the stroke events and its recurrence the reason for this could not be explained .

MATERIALS AND METHOD

SETTING : **INPATIENTS,**
THANJAVUR MEDICAL COLLEGE HOSPITAL,
THANJAVUR

ETHICAL COMMITTEE APPROVAL : YES OBTAINED

DESIGN OF STUDY : **OBSERVATIONAL AND PROSPECTIVE**
SINGLE CENTRED STUDY

PERIOD OF STUDY : December 2013 to june 2014

SAMPLE SIZE : 50 PATIENTS

SELECTION OF PATIENTS

INCLUSION CRITERIA

PATIENTS WITH YOUNG STROKE

EXCLUSION CRITERIA :

young stroke patients with the following risk factors were excluded from the study. Patients with

1. DIABETES MELLITUS

2.HYPERTENSION

3. SMOKING

4. ALCOHOLISM

5.HYPERLIPEDEMIA

STUDY METHODOLOGY

50 patients with young stroke were selected for the study. Patients having Conventional risk factor like hypertension ,diabetes mellitus, smoking, hyperlipedemia, alcoholism were excluded from the study

Diagnosis of stroke was based on history ,clinical features, ct brain and in some patients MRI brain.

The following investigations were done on admission:

1.complete blood count

2.random blood sugar

3.serum cholesterol

4.serum triglyceride

5.blood urea

6.serum creatinine

7.fasting serum homocysteine level

8.HIV

9.VDRL

10.ECG

11.CT BRAIN

12.CAROTID DOPPLER

13.ECHOCARDIOGRAM

MEASUREMENT OF SERUM HOMOCYSTEINE:

Serum homocysteine is measured by fluorescein polarization immunoassay(FPIA)

Principle of the procedure:

First the bound homocysteine present in serum is reduced by the use of dithiothreitol(DTT).then the free homocysteine is converted to S- adenosyl homocysteine (SAH) by the use of enzyme S-ADENOSYL homocysteine hydrolase and adenosine

HOMOCYSTENE +ADENOSINE $\rightleftharpoons$ SAH + H_2O

This mixture containing SAH , antibody , FPIA diluents buffer and a tracer tagged with a fluorescent chromophore were added to the cuvette.there will be competition between SAH from the serum sample and the fluorescent tagged tracer to bind the antibody.then the intensity of the polarised light is measuredusing FPIA optical assembly

Specmen collection and storage :

4 ml of blood was collected in EDTA coated tubes.samples are stored at 2-8 degrees if testing is delayed.the serum is separated by centrifugation:

OBSERVATION AND RESULTS:

50 patients with young were included in the sudy. Serum homocysteine level were measured and results were analysed:

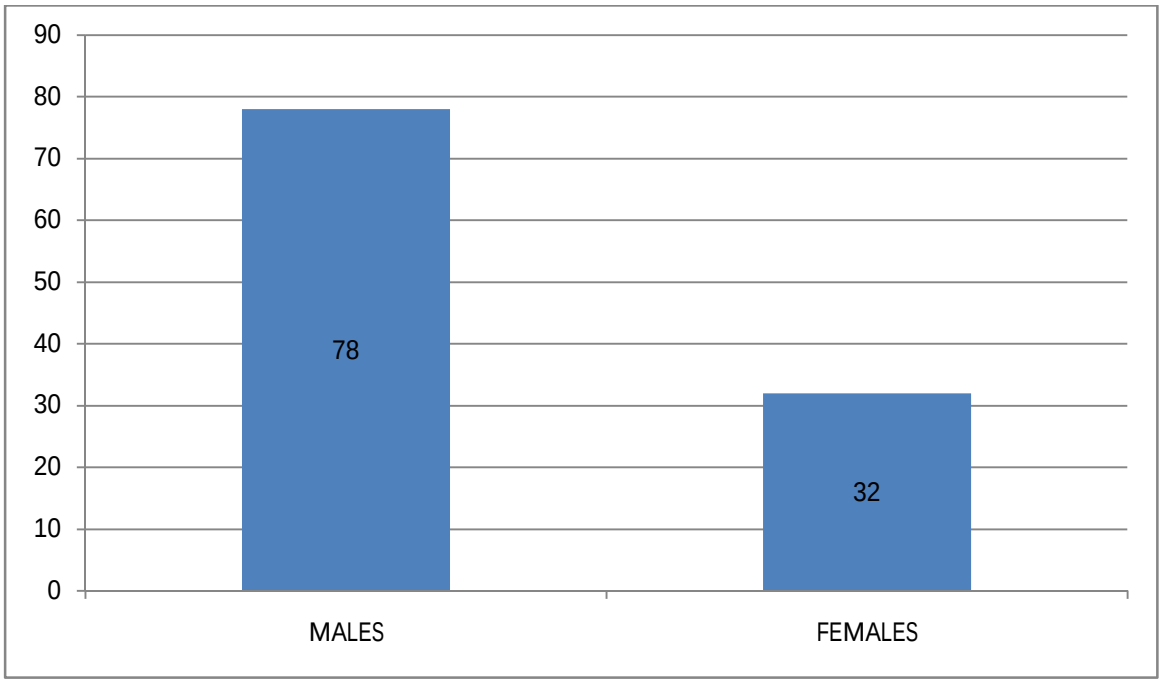
YOUNG STROKE PATIENTS :

50 young stoke patients were included in the study. Serum homocyteine levels were measured and results were analysed.among 50 patients 39 were males and 11 were females.male preponderenc was seen.

TABLE 1 SEX DISTRBUTION IN YOUNG STROKE PATIENTS

Sex	Number of patients	Percentage
Male	39	78
Female	11	22

Figure 11



AGE GROUP:

The maximum age limit of Patients included in the study were < 45. Mean age group of patients included in the study is 30.

TABLE 2 AGE DISTRIBUTION IN YOUNG STROKE PATIENTS

Age group	Number OF patients	Percentage%
15 - 20	2	4
20 - 25	5	10
25- 30	15	30
30- 35	19	38
35 - 40	5	10
40-45	4	8

Figure 12

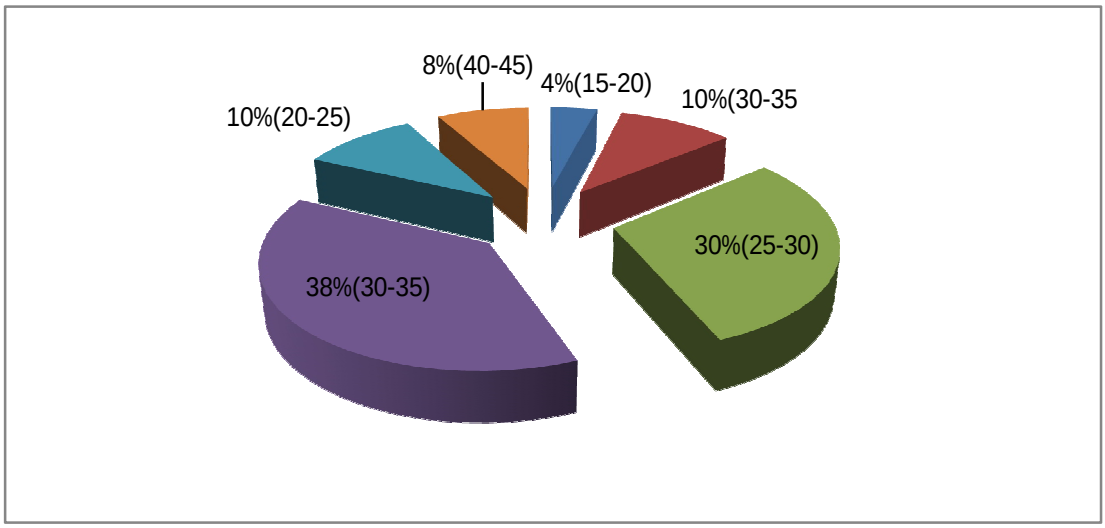
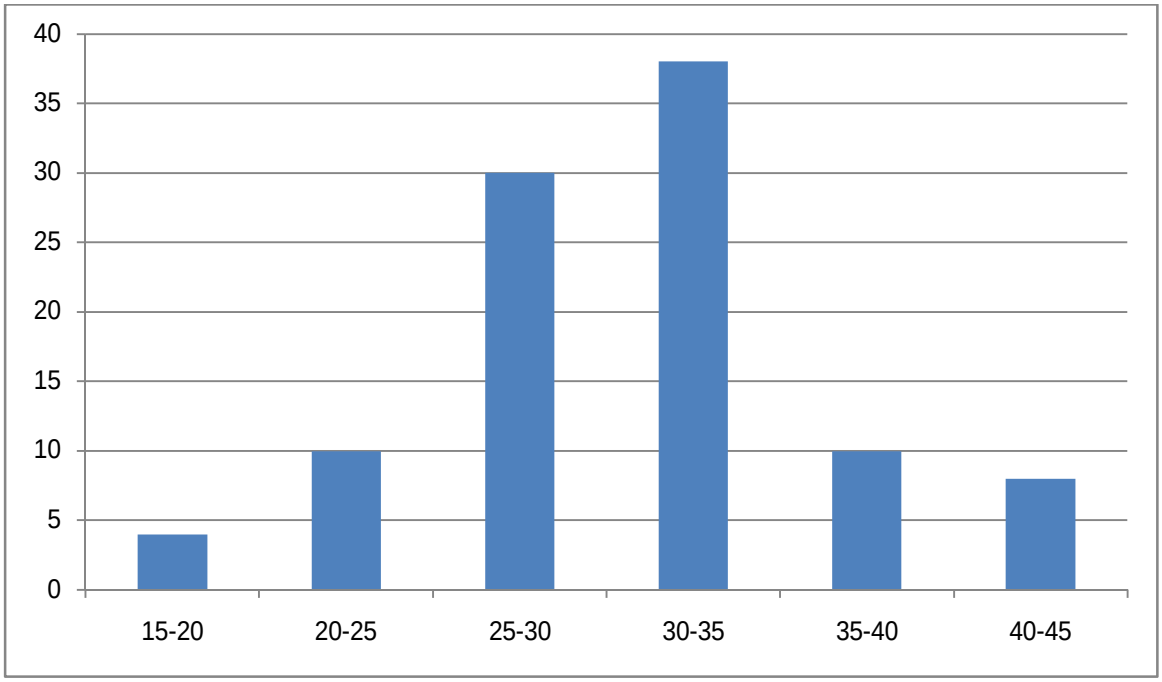


Figure 13



STROKE PATIENTS WITH ELEVATED HOMOCYSTEINE:

Of the 50 patients included in the study 32 patients had elevated homocysteine and 18 patients homocysteine were within normal limit. Hence the study shows an increased incidence of stoke in patients with elevated homocysteine.

TABLE 3 STROKE PATIENTS WITH ELEVATED HOMOCYSTEINE

SERUM HOMOCYSTEINE LEVEL	Number of patients	Percentage
NORMAL	18	36%
ELEVATED	32	64 %

Figure 14

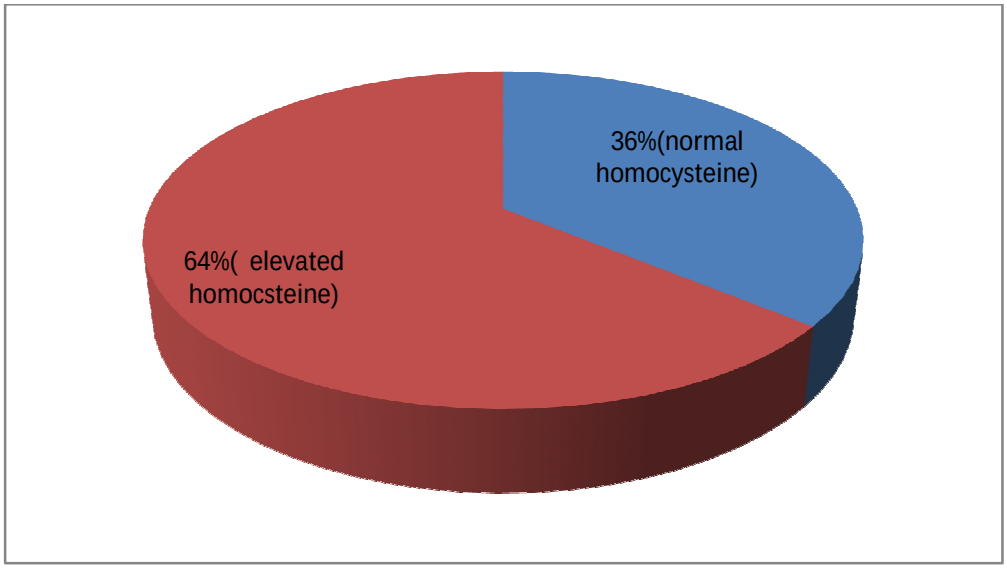


Figure 15

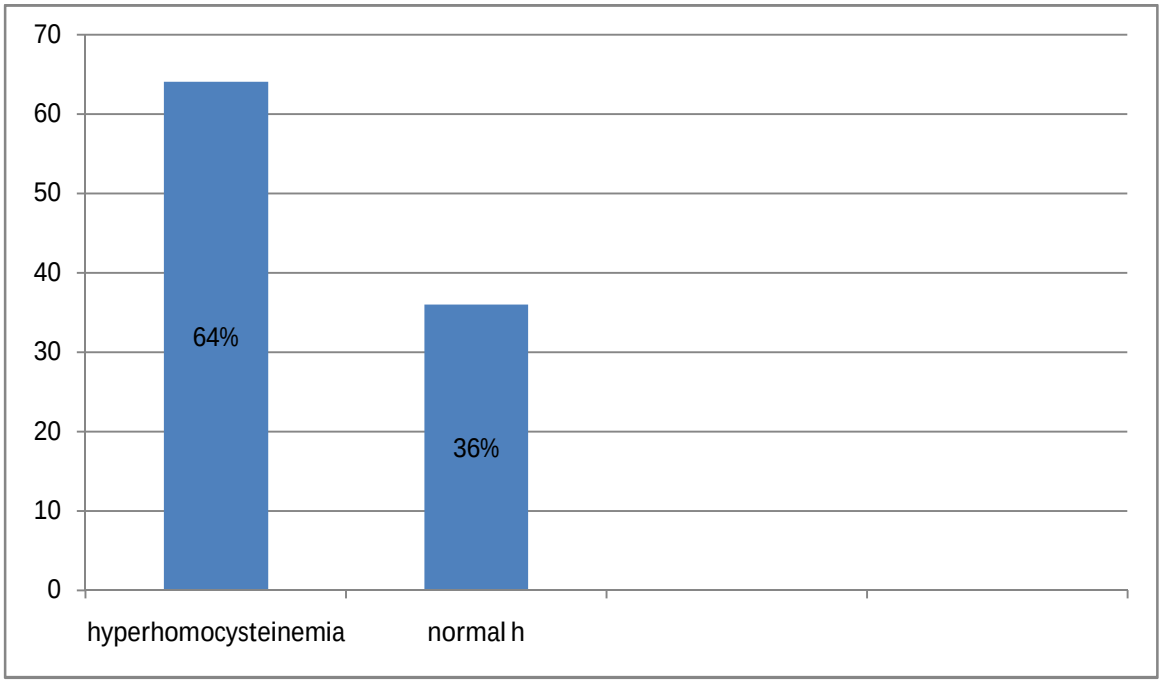


TABLE 4 Hyperhomocysteinemia statistical significance

Homocysteime	No.of respondents (n=50)	Percentage (100%)
Below 15	18	36.0
Above 15	32	64.0

TABLE 5 T-Test

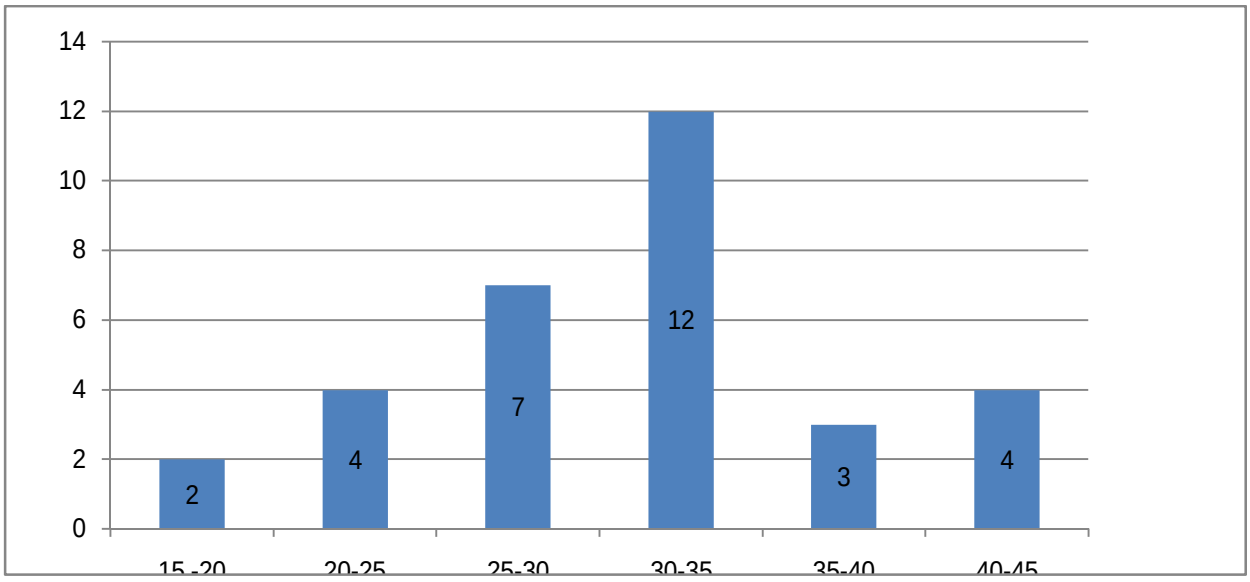
Homocysteime	Mean	S.D	Statistical inference
Below 15 (n=18)	7.9239	3.61025	T=-7.026 Df=48 .000<0.05 **Significant**
Above 15 (n=32)	32.0016	14.22459	

This shows it is statistically significant .

AGE DISTRIBTION OF HYPERHOMOCYSTEINEMIA: TABLE 6

Age group	No OF PATIENTS	Percentage
15 - 20	2	6.25
20 - 25	4	12.5
25- 30	7	21.85
30- 35	12	37.5
35 – 40	3	9.37
40-45	4	12.5

Figure 16



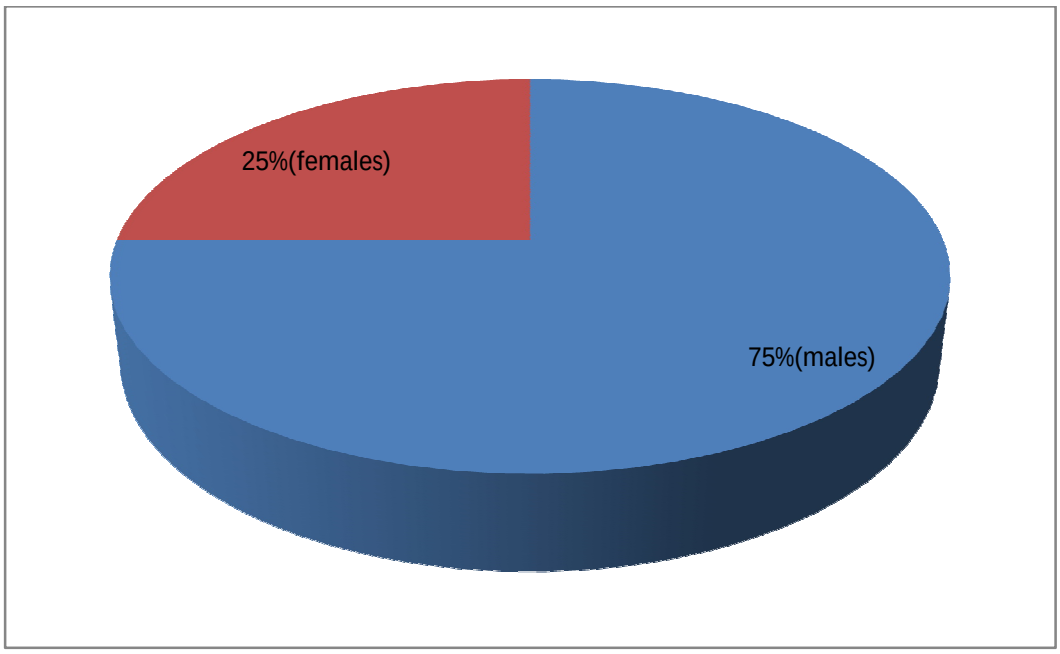
Sex distribution of patients with elevated homocysteine:

Among 32 patients(64%) with elevated homocysteine 24 were males and remaining 8 were females . this shows male preponderance.

TABLE 7 SEX DISTRIBUTION IN PATIENTS OF ELEVATED HOMOCYSTEINE

sex	no	Percentage
Male	24	75 %
Female	8	25%

Figure 17



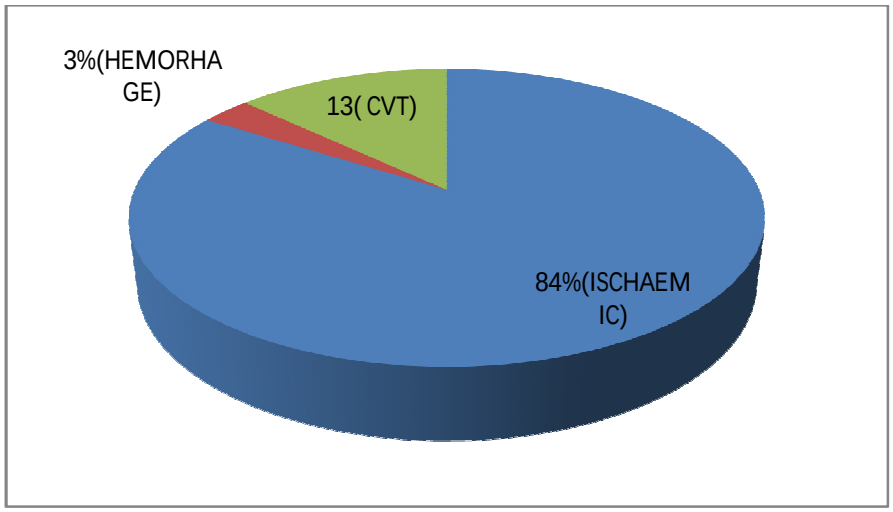
TYPE OF STROKE :

Young stroke Patients with elevated homocysteine had ischaemic, hemorrhagic stroke or cortical vein thrombosis. In our study out of 32 patients with elevated serum homocysteine there wsa 1 hemorhagic stroke 4 CVT, and the remaining 27 patients had ischaemic stroke.

TABLE 8 TYPE OF STROKE IN HYPERHOMOCYSTENEMIA GROUP

TYPE OF STROKE	NUMBER	PERCENTAGE
ISCHAEMIC	27	84%
HAEMORRHAGIC	1	3%
CORTICAL VENOUS THROMBOSIS	4	13 %

Figure 18



All the 4 patients with CVT in the elevated homocysteine group were females indicating CVT was more common among females in young stroke patients presenting as CVT.

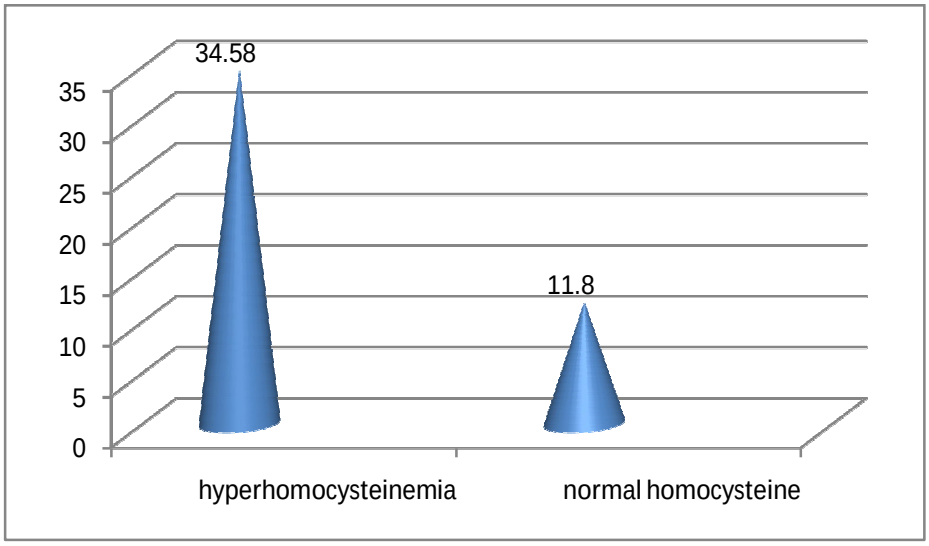
YOUNG STROKE PATIENTS WITH ELEVATED HOMOCYSTEINE VS NORMAL HOMOCYSTEINE :

Average serum homocysteine level in patients of young stroke with elevated homocysteine is 34.58 .the average homocysteine level in young stroke patients with normal range homocysteine is 11.8

TABLE 9 AVERAGE HOMOCYSTEINE LEVEL BETWEEN TWO GROUPS

HOMOCYSTEINE	AVERAGE HOMOCYSTEINE
ELEVATED GROUP	34.58
NORMAL GROUP	11.8

Figure 19



DISCUSSION

Many studies have showed that increased serum homocysteine level represents an independent risk factor for coronary, cerebrovascular and peripheral arterial disease.

Hyperhomocysteinemia is one of the newly recognized factor that increases the risk of vascular disease. Mechanisms by which hyperhomocysteinemia increases risk of cerebrovascular accidents are not clear, but several possible mechanisms have been proposed. Hyperhomocysteinemia is associated with atherosclerosis.

Experimental studies both in vivo and in vitro shows that homocysteine causes endothelial injury and cell detachment.

Measurement of homocysteine may become the integral part of workup of young stroke patients in future. Of the 50 patients studied 32 patients had elevated serum homocysteine and 18 patients had homocysteine within normal limit. This shows increased homocysteine was elevated in majority of young stroke patients without the conventional risk factors.

In our study hyperhomocysteinemia was more common in males compared to females . Our findings were consistent with study of Narang et al2, Modi et al6, Bogdan et al10 and Andrew et al published in neurology journal [53]. .

However Kang et al studies shows that young healthy women have homocysteine levels lower than healthy men. This difference diminishes with ageing. An abrupt increase in serum homocysteine in women after 50 years suggests that sex difference in homocysteine disappears with increasing age.

In our study of young stroke patients no of patients with infarct was around 86 percent and that of hemorrhagic stroke was 3 percent and that of CVT was 13percent. Our findings were consistent with study of Datta et al and Boysen et al where serum homocysteine levels were significantly raised in infarcts when compared to hemorrhage.

Clarke R et al, Olsegun et al, Osunkalu et al, Kittner et al, Bruce et al, Perry et al and Zongte et a concluded hyperhomocysteinemia as an independent predictor of stroke risk (both infarct and hemorrhage).

Modi et al, Roudbari et al and Nigel et al concluded that hyperhomocysteinemia as an important risk factor ischemic stroke [52].

Hyperhomocystenemia is associated with recurrent stroke according a journal published in Stroke. 2003 May;34(5):1258-61. Epub 2003 Apr by Boysen G[1], Brander T, Christensen H, Gideon R, [1]Department of Neurology, Bispebjerg Hospital, 2400 Copenhagen NV, Denmark [51].

Individuals with ischemic stroke and hyperhomocysteinemia may benefit from HLT(homocysteine lowering therapy) for secondary prevention according to VITATOPS .

In our study we excluded patients with conventional risk factors and included only patients without those risk factors and evaluvated whether hyperhomocysteinemia has a role independent risk factor for stroke.We found that significant number of patients had hyperhomocystenemia .hence hyperhomocstenemia is an emerging independent risk factor for stroke in our study.

CONCLUSION:

1) Our study shows hyperhomocystenemia in majority of young stroke patients around 64% who did not have the conventional risk factors like diabetes mellitus ,hypertension , hyperlipedemia, and other risk factors like smoking and alcohol.

2) Our study shows that young stroke patients with hyperhomocystenemia were more commonly found in the age group of 30-35 and the common age group of patients of young stroke with or without hyperhomocystenemia was also in the same age group.

3) Our study also shows that hyperhomocstenemia as a cause of young stroke was more common among males compared to females.

4) Since hyperhomocystenemia is associated with increased incidence of young stroke and recurrent stroke large group of well organized study studies has to be conducted to find out whether homocysteine lowering therapy with high dose folic acid,pyridoxine and vitamin b12 reduces the incidence of young stroke and recurrent stroke .

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CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR.K.SATHYASAGAR,** post graduate in department of internal medicine ,thanjavur medical college & hospital, thanjavur – 613001 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of participant

PROFOMA

A STUDY OF CLINICAL PROFILE AND SERM HOMOCYSTEINE LEVEL- YOUNG STROKE EXCLUDING THE RISK FACTORS SMOKING, ALCOHOL, HYPERCHOLESTROLEMIA,HYPERTENSION,DIABETES MELLITUS.

NAME : IP :

AGE : DOA: DOD:

PRESENTING ILLNESS:

PAST HISTORY:

DIABETES :

HYPERTENSION :

STD :

PERSONAL HISTORY

SMOKING :

ALCOHOLISM :

FAMILY HISTORY :

OTHERS :

CLINICAL EXAMINATION:

GENERAL EXAMINATION:

BP PR:

CNS:

HMF :

CRANIAL NERVES:

MOTOR: POWER BULK TONE DTR

R

L

SENSORY SYSTEM:

SPINE AND CRANIUM:

CVS:

RS: **ABDOMEN:**

RS:

PA:

INVESTIGATIONS

CBC: BLOOD SUGAR :

HB-

RBS -

TC-

FBS -

DC-

PPBS -

PCV-

BLOOD UREA:

SERUM CREATININE:

ESR-

LIPID PROFILE :

PLATELET-

Sr cholesterol:

RBC TG:

HDL: LDL: VLDL

HIV:

VDRL:

ECG:

CT BRAIN:

MRI:

CAROTID DOPPLER:

SERUM HOMOCYSTEINE:

	NAME	*AGE*	*SEX*	*DIABETES*	*HYPERTENSION*	*SMOKING*	*ALCOHOLISM*	**HYPER LIPIDEMIA**	**RBS**	**SERUM CHOLESTEROL**	**TG**	**UREA**	**CREATININE**	**SERUM HOMOCYTEINE**	**VDRL**	**HIV**	**ECG**	**CT BRAIN**	**MRI**	**CAROTID DOPLER**	**ECHO**	**URINE ALBUMIN**	**URINE SUGAR**	**URINE DEPOSITS**	**HEMOG**	**BP**
1	marimuthu	35	m	no	no	no	no	no	87	170		24	0.6	16.3	NR	WNL	wnl	infarct		NO RWMA	NIL	NIL	NIL		11	120/70
	rajini	34	m	no	no	no	no	no	110			36	1.2	22.4		nr	wnl	infarct			no rwmA	nil	nil	nil	9	140/90-
3	vajithabanu	22	f	no	no	no	no	no	100	160	116	26	0.8	24.3	nr	nr	wnl	infarct	infarct	normal	no rwma	nil	nil	nil	10	100/60
4	kavitha	24	f	no	no	no	no	no	134	155	140	42	0.9	42.7	nr	nr	wnl	wnl	infarct ant	normal	norwma	nil	nil	nil	10	130/90
5	ayyapan	26	m	no	no	no	no	no	112	155	123	45	1	36.8	nr	nr	wnl	infarct	infarct	normal	wnl	nil	nl	nl	12	120/70
6	durai	29	m	no	no	no	no	no	95	143	145	26	0.9	17	nr	nr	wnl	infarct		normal	normaL	NIL	NIL	nil	9	150/100
7	stella marry	30	m	no	no	no	no	no	100	136	120	34	1.2	33	nr	nr	wnl	cvt	sst	normal	normal	nil	nil	nil	7.8	120/90
8	manikandan	36	m	no	no	no	no	no	112	120	110	28	0.9	26	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	11	110/80
9	kamal raj	27	m	no	no	no	no	no	98	150	128	38	0.7	7.13	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	8	120/70
10	raja	30	m	no	no	no	no	no	100	176	120	40	0.9	12	nr	nr	wnl	infarct		normal	normal	nil	nl	nil	9	130/90
11	ajith	16	m	no	no	no	no	no	88	150	144	24	1	45	nr	nil	wnl	infarct		normal	normal	nil	nl	nil	11	120/70
12	aparna	20	f	no	no	no	no	no	100	112	110	32	0.7	11	nr	nil	wnl	infarct		normal	normal	nil	nil	nil	12	130/90
13	vijaguru	30	m	no	no	no	no	no	112	156	128	27	0.6	32.12	nr	nr	wnl	infarct		normal	normal	NIL	NIL	NIL	10	110/70
14	kamal	30	m	no	no	no	no	no	207	112	110	42	0.9	42.12	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	7.6	100/60
15	selvaraj	29	m	no	no	no	no	no	118	134	112	34	1.2	12	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	12	108/80
16	jayalakshmi	26	f	no	no	no	no	no	120	160	120	38	1.4	70.8	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	8	120/90

	NAME	AGE	SEX	DIABETES	HYPERTENSION	SMOKING	ALCOHOLISM	HYPER LIPIDEMIA	RBS	SERUM CHOLESTEROL	TG	UREA	CREATININE	SERUM HOMOCYTEINE	VDRL	HIV	ECG	CT BRAIN	MRI	CAROTID DOPLER	ECHO	URINE ALBUMIN	URINE SUGAR	URINE DEPOSITS	HEMOG	BP
17	ramkumar	33	m	no	no	no	no	no	112	128	130	39	1	52.96	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	10	110/70
18	pandiyaraj	42	m	no	no	no	no	no	78	120	130	22	0.7	10	nr	nr	wnl	infarct		normal	normal	NIL	NIL	NIL	10	120/80
19	mohammed aslam	32	m	no	no	no	no	no	88	112	155	26	0.6	3.26	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	11	110/80
20	kamaraj	24	m	no	no	no	no	no	98	140	160	40	0.8	42.42	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	8	110/80
21	surya prakash	24	m	no	no	no	no	no	120	120	145	48	1.5	24	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	12	140/8
22	latha	32	f	no	no	no	no	no	128	120	124	52	1	27.8	nr	nr	wnl	infarct		normal	normal	nil	nil	nil		130/80
23	lakshmi	26	f	no	no	no	no	no	100	140	140	36	1.3	12.8	nr	nr	wnl	?cvt	cvt	normal	normal	nil	nil	nil	10	100/60
24	sekar	40	m	no	no	no	no	no	106	128	140	36	2	32.3	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	11	110/70
25	chinapan	28	m	no	no	no	no	no	82	140	160	27	1.4	11.6	nr	nr	wnl	infarct		normal	normal	NIL	NIL	NIL	9	120/90
26	bakyaraj	32	m	no	no	no	no	no	91	112	150	44	0.4	40	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	8	130/90
27	ramakrishnan	25	m	no	no	no	no	no	110	130	170	42	0.9	2	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	9	120/80
28	joseph sagayaraj	33	m	no	no	no	no	no	132		140	40	1	22.4	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	10	140/90
29	fathima	28	f	no	no	no	no	no	100	148	140	33	1	66.4	nr	nr	wnl	wnl	cvt	normal	normal	nil	nil	nil	11	130/90
30	govindaraj	37	m	no	no	no	no	no	76	180	140	36	1	18.9	nr	nr	wnl	infarct		normal	normal	NIL	NIL	NIL	10	126/90
31	tamiarasan	33	m	no	no	no	no	no	120	170	150	29	1	22.3	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	9	110/80
32	lakshmana	29	m	no	no	no	no	no	88	162	130	45	0.8	4.2	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	9	120/70

	NAME	*AGE*	*SEX*	*DIABETES*	*HYPERTENSION*	*SMOKING*	*ALCOHOLISM*	HYPER LIPIDEMIA	RBS	SERUM CHOLESTEROL	TG	UREA	CREATININE	SERUM HOMOCYTEINE	VDRL	HIV	ECG	CT BRAIN	MRI	CAROTID DOPLER	ECHO	URINE ALBUMIN	URINE SUGAR	URINE DEPOSITS	HEMOG	BP
33	appadrai	40	m	no	no	no	no	no	98	150	128	35	0.7	32.6	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	10	110/60
34	pandiyan	34	m	no	no	no	no	no	103	160	140	44	0.7	30.3	nr	nr	wnl	hemorh age		normal	normal	nil	nil	nil	11	120/80
35	charlatha	26	f	no	no	no	no	no	110	170	10	48	0.9	28.63	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	12	130/80
36	bharathi	32	f	no	no	no	no	no	102	156	130	37	1.3	18.6	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	10	110/70
37	GOPINATH	26	M	no	no	no	no	no	115	142	120	38	1	18.72	nr	nr	wnl	infarct		normal	normal	NIL	NIL	NIL	10	120/80
38	HARISH	18	M	no	no	no	no	no	110	145	130	26	0.8	55.42	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	10	100/60
39	ARPUTHARAJ	31	M	no	no	no	no	no	110	170	120	27	0.7	18.76	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	11	108/70
40	RAJA	27	M	no	no	no	no	no	120	188	110	28	0.6	22	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	10	`110/70
41	elangovan	37	m	no	no	no	no	no	97	210	169	22	0.6	7.51	nr	nr	wnl	hemorh age		normal	normal	nil	nil	nil	9	120/80
42	megaraj	32	m	no	no	no	no	no	87		122	43	0.7	8.36	nr	nr	wnl	infarct		normal	normal	NIL	NIL	NIL	10	140/90
43	veeramani	34	M	no	no	no	no	no	100	166	130	43	0.8	11.4	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	10	120/80
44	mohamedibrahim	30	m	no	no	no	no	no	76	180	140	27	0.9	9.2	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	8	110/60
45	manivel	27	m	no	no	no	no	no	89	144	115	32	1.4	3.26	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	9	110/80
46	munusamy	39	m	no	no	no	no	no	110	178	136	40	1.2	7.51	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	8	120/90
47	sivanandham	30	m	no	no	no	no	no	100	159	137	25	1.8	2.56	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	11	112/80
48	mthlakshmi	28	f	no	no	no	no	no	84	170	138	30	1	6.84	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	12	120/90

	NAME	*AGE*	*SEX*	*DIABETES*	*HYPERTENSION*	*SMOKING*	*ALCOHOLISM*	**HYPER LIPIDEMIA**	**RBS**	**SERUM CHOLESTEROL**	**TG**	**UREA**	**CREATININE**	**SERUM HOMOCYTEINE**	**VDRL**	**HIV**	**ECG**	**CT BRAIN**	**MRI**	**CAROTID DOPLER**	**ECHO**	**URINE ALBUMIN**	**URINE SUGAR**	**URINE DEPOSITS**	**HEMOG**	**BP**
49	pakirisamy	41	m	no	no	no	no	no	88	166	120	28	1	22	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	12	110/80
50	poovarasu	34	m	no	no	no	no	no	102	145	135	32	0.9	19	nr	nr	wnl	infarct		normal	normal	nil	nil	nil	10	